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SPEECHES, ARTICLES, AND SELECTED PAPERS

By

James B. Wyngaarden, M.D.

1982-1988

Volume 1 (of 5)

(April 19, 1982—April 10, 1983)

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Speeches, Articles, and Selected Papers
James B. Wyngaarden, M.D.

1982-1988
Volume 1

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INHERITED DISORDERS OF PURINE METABOLISM*

by

James B. Wyngaarden, M.D.**

Seven well-established inborn errors of purine metabolism are summarized in Table 1 according to the major manifestations of each enzyme abnormality. These are hypoxanthine phosphoribosyl-transferase deficiency, phosphoribosylpyrophosphate synthetase superactivity, xanthine oxidase deficiency, adenine phosphoribosyltransferase deficiency, myoadenylate deaminase deficiency, and adenosine deaminase and purine nucleoside phosphorylase deficiencies. An additional disorder, glucose 6-phosphatase deficiency, is included even though glucose 6-P'tase is not really a purine enzyme, because its deficiency results in a marked secondary derangement of purine metabolism. Each of these conditions will be summarized briefly.

Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) Deficiency.[1] The discovery of a virtually complete deficiency of hypoxanthine and guanine phosphoribosyltransferase activities in the erythrocytes of patients with the Lesch-Nyhan syndrome by Seegmiller et al. in 1964[2] ushered in what Lesch[3] has called

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"the purine revolution." The Lesch-Nyhan syndrome is characterized by chorioathetosis, spasticity, mental retardation, severe self-mutilation, and marked hyperuricemia and hyperuric-aciduria. Renal stones and renal failure are common and gouty attacks may occur. The condition is X-linked and involves only male children. Life expectancy is markedly shortened but some patients have lived into their twenties with allopurinol and supportive therapy.

The consequences of HPRT deficiency will become clear from a brief review of normal purine synthesis and catabolism (Fig 1). The first specific reaction of purine biosynthesis involves an interaction of glutamine and phosphoribosylpyrophosphate (PP-ribose-P) to form phosphoribosylamine. This compound then undergoes several sequential reactions that eventually result in the formation of inosine monophosphate (IMP), the first complete purine compound. IMP may be converted to adenosine monophosphate (AMP) or guanosine monophosphate (GMP) which are precursors of coenzymes and of nucleic acids. They are also regulators of activity of the first enzyme of the pathway (amidophosphoribosyl-transferase) as endproduct or feedback inhibitors of purine biosynthesis. AMP and GMP may also be broken down to ribonucleo-side compounds and eventually to free bases hypoxanthine and guanine which are more direct precursors of uric acid. But not all of hypoxanthine and guanine is lost as uric acid; these bases are normally extensively reclaimed and reconverted to nucleotide stages by couplings with PP-ribose-P. In man, the reactions of

PP-ribose-P with hypoxanthine and guanine are catalyzed by a single enzyme, hypoxanthine-guanine phosphoribosyltransferase, usually called simply HPRT. A similar salvage reaction with adenine is catalyzed by a different enzyme.

HPRT deficiency leads to a block in the salvage of hypoxanthine and guanine and also to accumulation of the PP-ribose-P not used in the absent phosphoribosyltransferase reaction. Hypoxanthine and guanine are quantitatively converted to uric acid, and in addition the excess levels of PP-ribose-P lead to increased rates of purine biosynthesis de novo and further loss of purine bases. The result is marked hyperuricemia and hyperuricaciduria.

In most patients with the Lesch-Nyhan syndrome the residual amounts of HPRT are too low to be detected by immunological means and the enzyme may be absent altogether. However, in other instances the deficiency is attributable to molecular alterations that result in altered affinities of the enzyme for a substrate or in altered catalytic reaction rates. In these instances immunological cross-reactive material is found, and in some cases an approximately normal amount of enzyme protein is present, though non-functional under physiological conditions. At least 5 such variants are known. They have been named for the cities of origin of the patients, e.g., HPRT Kinston, by analogy with hemoglobin nomenclature. Studies are underway in several laboratories to establish the amino acid sequences of these enzymes or the nucleotide sequences of their genes.

When the genetic alteration of the enzyme allows some residual HPRT activity under physiological conditions, the severe manifestations of the Lesch-Nyhan syndrome do not appear and a syndrome known as "partial HPRT deficiency" results. This syndrome has as its chief manifestation marked hyperuricemia and gout or kidney stones at a relatively young age, and may occasionally be accompanied by a neurological disorder resembling spinocerebellar ataxia, but mental deficiency and compulsive self-injury are absent. Since the HPRT gene is X-linked, this disorder is also restricted to males, but some female heterozygotes do show HPRT values intermediate between those of normal and affected subjects, and may have hyperuricemia or hyperuricaciduria, and may develop gout in later life. HPRT values in males with the partial HPRT deficiency syndrome range from 0.2 to 30 percent of normal. Clearly the molecular alterations must be heterogeneous. Partial HPRT deficiency appears to account for about 0.5 percent of adult gout.

PP-ribose-P Synthetase Superactivity.[4] Screening of gouty patients with marked hyperuricemia and hyperuricaciduria disclosed some who had normal HPRT activity. Sperling[5] found one such subject who also had elevated erythrocyte levels of PP-ribose-P, and correctly surmised a primary increase in its rate of synthesis. He showed that PP-ribose-P synthetase was superactive at low phosphate levels compared with the enzyme from normal subjects. PP-ribose-P synthetase catalyzes the reaction of ribose 5-phosphate and ATP to form PP-ribose-P. The enzyme

requires inorganic phosphate as an obligatory allosteric activator, and is normally inhibited by ADP (which competes with ATP) and by purine nucleotides in general (metabolic pool inhibition). The mutant enzyme discovered by Sperling had reduced affinities for nucleotide regulators in general and presumably was overactive under physiologic conditions. This resulted in excess synthesis of PP-ribose-P and continuous stimulation of synthesis of phosphoribosylamine, purine ribonucleotides and uric acid. Severe gout or kidney stones occur at an early age. The gene for PP-ribose-P synthetase is also X-linked, and the patients are males, except that one female heterozygote is also known to be affected.

Although the total number of families known to have superactive variants of PP-ribose-P synthetase is small, at least 4 sub-types of this condition are known (Table 2). In addition to Type I described by Sperling, Becker and colleagues have reported patients with increased enzyme activity per molecule (Type II), with enzyme showing increased affinity for its substrate ribose 5-phosphate (Type III) or with a combination of Types I and II (Type IV).

Xanthine Oxidase Deficiency.[6] In this condition there is a block in the reaction that normally oxidizes hypoxanthine to xanthine and xanthine to uric acid. Usually the block is virtually complete but some patients appear to have a few percent of residual activity. Studies are limited by the distribution of

the enzyme activity which is restricted to liver and small intestinal and rectal mucosa and colostrum or breast milk in the human. About 50 cases are known, many coming from the Mediterranean basin, especially from Lebanon and Spain. In this condition xanthine and hypoxanthine replace uric acid as the end products of purine metabolism. Urinary xanthine levels may be high enough to lead to xanthine stone formation. Some patients have developed a late-onset type of myopathy associated with xanthine crystals in muscle and a few have had episodes of acute arthritis suggested to be "xanthine gout," but this is not proven. About half of all known patients were asymptomatic, having been diagnosed following detection of a serum urate level of under 1.0 mg/dl.

A new condition has been recognized in an infant with combined xanthine oxidase and sulfite oxidase deficiencies due to an absence of a common cofactor containing molybdenum. The defect appears to involve an inability to synthesize the pteridyl moiety of the cofactor. Clinically, there was severe neurological dysfunction.

Adenine Phosphoribosyltransferase (APRT) Deficiency.[7] APRT normally catalyzes a salvage reaction in which adenine condenses with PP-ribose-P to form AMP. In subjects with APRT deficiency, adenine accumulates and is oxidized via the 8-hydroxy intermediate to 2,8-dihydroxyadenine (2,8-DHA) which is excreted in excessive amounts. 2,8-DHA is highly insoluble and may form

renal stones. In APRT deficiency adenine metabolites may amount of 20-30 percent of the total purine excretion even on a low purine diet. The source of the endogenous adenine is probably the polyamine pathway of which adenine is a metabolic by-product; phosphorolysis of adenosine is probably only a minor contributor. The gene coding for human APRT is located on the long arm of chromosome 16. Heterozygote frequency has been estimated at 0.4 to 1.1 percent in several population studies. This suggests that homozygosity may be more frequent than presently recognized. At least 18 instances of homozygous APRT deficiency have been reported since the disorder was identified in 1974, most of them in Japan. Five of the 18 have been adults. Several patients had earlier been thought to have uric acid stones, as 2,8-DHA has spectral and chemical properties rather like those of uric acid, but the compounds can be distinguished by ultraviolet, infrared and mass spectrometry. Treatment consists of a low purine diet and allopurinol.

Myoadenylate Deaminase Deficiency.[8] In 1978 Fishbein et al.[9] described five patients with a history of skeletal muscle dysfunction following exercise in whom adenylate deaminase activity was virtually absent from muscle. Over 20 additional patients have now been described. During normal exercise ATP is dephosphorylated and the product AMP is deaminated with release of NH_3. IMP accumulates in muscle and is reconverted to AMP in the purine nucleotide cycle, the enzymes of which are particularly active in skeletal muscle. In myoadenylate

deaminase deficiency, exercise does not release NH_3 into the blood stream; this provides the basis for a presumptive diagnostic test. AMP rather than IMP accumulates with exercise, and is subject to nucleotidase action; adenosine, inosine and hypoxanthine are formed and are lost from the muscle. The concentration of total adenyl nucleotides falls markedly and remains depressed for hours.[10] Since ATP is the only source of energy for muscle contraction these observations may account for the post-exercise symptoms in these patients. The types of muscle dysfunction, and age of onset, have shown wide variation. The condition is probably not rare: about 2 percent of muscle biopsy specimens accumulated in 3 centers for study of muscle disease showed myoadenylate deaminase deficiency. The condition shows autosomal recessive inheritance.

Adenosine Deaminase (ADA) and Purine Nucleoside Phosphorylase (PNP) Deficiencies.[11] Inherited deficiency of either ADA or PNP causes abnormalities of purine nucleoside metabolism that are selectively toxic to lymphocytes and result in severe immune deficiency disease in the neonatal period. Most patients with ADA deficiency lack both cell-mediated (T-cell) and humoral (B-cell) immunity and have severe combined immunodeficiency disease (SCID). Approximately 40 to 50 cases of ADA deficiency have been detected; about 30 percent of known cases of SCID are due to ADA deficiency. PNP-deficient children have a severe defect of cell-mediated immunity but humoral immunity is relatively normal. Nine cases of PNP deficiency have been reported. Both conditions

are inherited in an autosomal recessive manner. In ADA deficiency, adenosine and deoxyadenosine levels are elevated in plasma or urine, and dATP accumulates in erythrocytes and peripheral blood mononuclear cells. dATP is believed to accumulate preferentially in ADA-deficient T lymphocytes and to inhibit ribonucleotide reductase, thereby interfering with DNA synthesis. A second hypothetical mechanism invokes accumulation of S-adenosylhomocysteine secondary to adenosine increases, and inhibition of S-adenosylmethionine-mediated transmethylation reactions vital to lymphocyte division and function. In PNP deficiency dGTP accumulates in T lymphocytes. The resultant inhibition of ribonucleotide reductase and DNA replication has been proposed as an explanation of the T-cell defect in PNP deficiency.

Glucose-6-Phosphatase (G6P'tase) Deficiency.[4] Patients with G6P'tase deficiency (von Gierke's disease) can metabolize exogenous or gluconeogenetic glucose to glycogen or lactate, but cannot release free glucose from glucose 6-phosphate in response to hypoglycemia. Glycogen breakdown in response to hypoglycemia consumes inorganic phosphate; the drop in intracellular phosphate is proposed to release adenylic deaminase from its normally inhibited state, with resultant loss of adenyl nucleotides and conversion of the purines to uric acid. The drop in intracellular nucleotide levels is postulated to result in release of the first enzyme of purine biosynthesis (amidophosphoribosyltransferase) from inhibition, resulting in a compensatory

increase in purine biosynthesis de novo. These postulates could explain both the hyperuricemia and hyperuricaciduria of von Gierke's disease and the evidence for increased purine biosynthesis de novo.

Hepatic Adenylic Acid Deaminase Variant in Primary Gout. Hers and Van den Berghe[12] have postulated a similar mechanism in primary gout associated with increased carbohydrate intake, except that they suggest the presence of an AMP-deaminase variant that is less than normally sensitive to phosphate or GTP inhibition. One deceased gouty patient has been described in whose liver appropriate studies of sensitivity of AMP-deaminase to phosphate and GTP inhibition supported this hypothesis.[13] This defect, if widely distributed in the population, might explain much of what is now generally termed "idiopathic gout."

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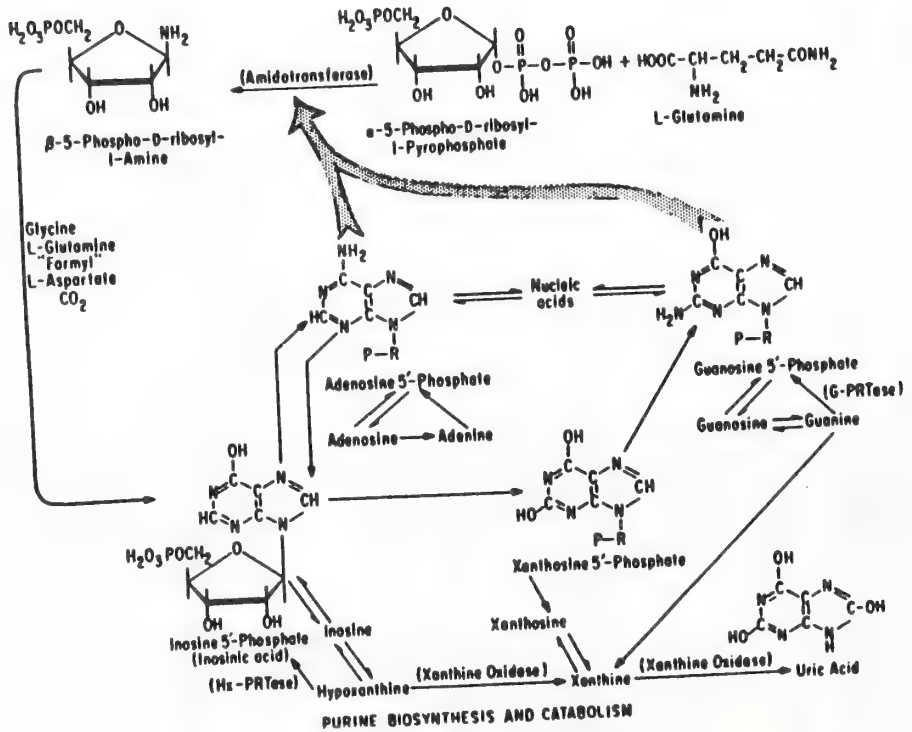
β-5-Phospho-D-ribosyl-1-Amine
(Amidotransferase)
α-5-Phospho-D-ribosyl-1-Pyrophosphate
L-Glutamine
Glycine
L-Glutamine
"Formyl"
L-Aspartate
CO2
Nucleic acids
Adenosine 5'-Phosphate
Adenosine
Adenine
Guanosine 5'-Phosphate
(G-PRTase)
Guanosine
Guanine
Xanthosine 5'-Phosphate
Xanthosine
Inosine 5'-Phosphate
(Inosinic acid)
Inosine
(H2-PRTase)
Hyposanthine
(Xanthine Oxidase)
Xanthine
(Xanthine Oxidase)
Uric Acid
PURINE BIOSYNTHESIS AND CATABOLISM

FIGURE 1

PP–RIBOSE–P SYNTHETASE VARIANTS

TYPE 1. REDUCED SENSITIVITY TO NUCLEOTIDE INHIBITORS

TYPE 2. INCREASED SPECIFIC ACTIVITY PER ENZYME MOLECULE

TYPE 3. INCREASED AFFINITY FOR RIBOSE-5-PHOSPHATE

TYPE 4. COMBINATION OF TYPES 1 AND 2

TABLE 2

INBORN ERRORS OF PURINE METABOLISM

Enzyme Deficiency	MANIFESTATIONS				
	Arthropathy	Renal Stone	Renal Failure	Myopathy	Immuno-deficiency
HGPRT	+ (Gout)	+	+		
PP-Ribose Synthetase ↑	+ (Gout)	+	+		
Xanthine Oxidase	+	+		+	
Adenine PPT		+	+		
Myoadenylate Deaminase				+	
Adenosine Deaminase					+
Purine N'Side Phosphorylase					+
Glucose G-P'tase	+ (Gout)	+	+	+	

TABLE 1

FOR RELEASE UPON DELIVERY

STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR-DESIGNATE
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH & HUMAN SERVICES

BEFORE THE

SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

APRIL 21, 1982

Mr. Chairman and Members of the Committee:

I appreciate the opportunity to discuss with you today the background and views I bring to the Directorship of the National Institutes of Health. I consider it a great honor to have been nominated by the President for this important position. And I want to assure you that I share with the Members of this Committee a high regard for the tradition of excellence in research and service to humanity exemplified by NIH. In assuming the post of NIH Director, my primary aim would be to nurture and enhance that tradition.

Having been personally and professionally associated with NIH in various connections for many years, I am no stranger to the institution. Nevertheless, I am quick to admit there is much to learn. I have, of course, developed a perspective toward NIH and its programs during a career in medicine and biomedical science as researcher, teacher, and administrator. I am familiar with the headaches and heartaches as well as the great satisfactions that come with work in the health sciences.

In recent weeks I have been doing my homework on the programs, policies, and issues before NIH. In that crash course, I have been helped greatly by the officers and staff of NIH and of the Department of Health and Human Services.

In that connection, I would like publicly to express my gratitude to Secretary Schweiker who has been most helpful to me with his wise counsel,

based on long experience in government and health matters. I appreciate his support and encouragement.

I am also grateful for the helpful advice received from Dr. Brandt and from Dr. Malone, Acting Director of NIH, and Dr. Joseph Rall, the Acting Deputy Director for Science.

And certainly, I want to thank the Members of this Committee for meeting with me and discussing NIH issues prior to today's hearing.

As mentioned earlier, I have had an association with NIH in various positions through the years. It could scarcely be otherwise, since NIH plays a unique and wide-ranging role in the field of biomedical research. Most recently, I have served as Hanes Professor and Chairman of the Department of Medicine at the Duke University School of Medicine. I have held that post for some 15 years, previously having served in various teaching, research, and administrative capacities at Duke and the University of Pennsylvania School of Medicine.

More specifically, in relation to NIH, I have conducted research in its Heart Institute and in what was then called the National Institute of Arthritis and Metabolic Diseases; I also served on the Board of Scientific Counselors to the latter Institute.

In addition, I have served as a member of the NIH Cardiovascular and General Medicine Study Sections and as Chairman of the Medical Scientist

Training Committee when the MD/PhD Program was initiated. I also served as consultant to the White House Office of Science and Technology Policy, as a member of the President's Science Advisory Committee and as Vice Chairman of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel of the National Research Council, and as Executive Committee Member of its Assembly of Life Sciences.

As you will gather from that brief account and a review of the curriculum vitae before you, my path has crossed that of NIH many times since graduation from the University of Michigan School of Medicine. During my professional life in basic and clinical research and in the training of future physicians and scientists, I have encountered the spectrum of problems and opportunities in biomedicine. I have enjoyed work in the health sciences during a period of explosive growth of knowledge.

In all candor, I must tell the Committee that I did not actively seek the post of Director of NIH; I was personally and professionally content with my work at Duke. At the same time, however, I must emphasize the mixed sense of pride and awe I feel at being considered for the select company of distinguished scientists who have served as Director of NIH.

An underlying theme in my acceptance of that honor is a sense of obligation based on an awareness of the vital role of NIH in biomedical research, and its support of my work and the institutions with which I have been associated. Along with Duke University, I have benefited from the programs of NIH; I feel that service in this unique institution will

constitute some measure of repayment. I welcome the opportunity to make a contribution to NIH and its mission.

I would now like to discuss some general views and basic principles concerning biomedical research and issues facing NIH.

I am well aware that this is a critical period for NIH and the field of biomedical research. The explosion of biomedical knowledge and improved technology in recent years offers greater opportunity for advances in medicine and health than ever before. At the same time, we must face the reality of economic constraints.

I am strongly committed to the pursuit of basic research as the foundation for the understanding, treatment, and prevention of disease and disability. Equally, I believe that investigator-initiated research holds the greatest promise for significant discoveries. History clearly shows that the great advances come through hard work by dedicated individuals and teams pursuing their own creative ideas.

In regard to basic research, I share the view of Dr. Lewis Thomas who wrote last year in the New England Journal of Medicine that:

> We are beginning to draw from a bank of stored information in biomedical science, and I suspect that we are doing something like this in the physical sciences as well. There is some danger that the need to continue depositing new information in that bank will be overlooked in the pressure for quick applications . . . If things go on in this way, the country's basic science effort will come to a standstill, and the bank will go empty.

One of my major goals as Director will be to preserve the traditional emphasis of NIH on basic research and training as the bedrocks upon which all of the rest of its program structure is built.

The importance of basic research was underscored in a statement last December by the President's Science Advisor, Dr. George A. Keyworth, who said:

> . . . let me emphasize again that this Administration views basic research as a vital investment with a good return and believes that, as a contribution to overall national security and economic strength, we must maintain health across the spectrum of science, striving for excellence in all these fields.

Dr. Keyworth was speaking of science in general, but his statement applies equally to the biomedical sciences. A commitment to Federal support of basic research is apparent in my discussions with Secretary Schweiker and others in this Administration. As you know, the Secretary was an advocate for basic research and prevention when he was a member of this Committee, and he continues this view in his present capacity. I am sure that view is shared by this Committee, which has generously supported such work over the years. If you will permit, Mr. Chairman, I would also like to cite your remarks in introducing the Biomedical Research, Training and Medical Library Assistance Amendments of 1982. On that occasion you stated:

> Everyone, even critics of our national health policy, agrees that our Government's commitment to fund basic biomedical research has paid off handsomely. The results have been translated to improved health and medical care not only for our citizens, but also for people throughout the world.

As a corollary to emphasis on investigator-initiated research, I am also committed to support for research training, for both physician and Ph.D. research scientists. Clearly, if we are to have excellence and continuity in research, we must train scientists to carry on this work in the future.

I believe we must make every effort to maintain the momentum of scientific research and discovery achieved in recent decades, achievements based on many years of work in basic science. The intramural research program and the Clinical Center at NIH are key elements in the search for biomedical knowledge that extends across the Nation and throughout the world. Our recent advances in scientific understanding are being translated into medical practice and the result is improving health and well-being for all.

The kind of research necessary for such advances is highly complex, demanding well-trained investigators and sophisticated instruments. Not surprisingly, this work is expensive. And that fact, coupled with a need for budgetary restraint, places a high premium on sound decisions. Difficult choices are unavoidable and we must be prepared to make them.

We must set priorities wisely, emphasizing our investigator-initiated research and relying on the system of study sections and advisory councils by which we weigh proposals and monitor progress in research. We must continue to manage our programs for maximum efficiency and effectiveness as we invest in areas of high promise in pursuit of the NIH mission to understand, treat, and prevent disease and disability.

In conclusion, Mr. Chairman, I want to restate my awareness of the unique role that NIH plays in the health of our people and assure you of my commitment to its continuing service. Words I wrote two years ago seem appropriate here:

> I have confidence that the issues confronting us can be met and the problems solved. The stakes are high. Basic scientific knowledge in biology and medicine continues to expand at an awesome rate. The stock of usable knowledge is at an all-time high, and the opportunities for successful application of that knowledge to unsolved problems of health and disease have never been brighter. Great progress is being made, and the momentum must not be lost.

Mr. Chairman, I retain those views today and continue to believe, as I stated then, that "future medical historians will conclude that the Golden Age of medicine was not the two decades just passed, but the years that lie immediately ahead."

I thank you, Mr. Chairman and Members of the Committee, for the courtesies you have extended and for hearing me today. Frankly, I am eager to get on with the job and I look forward to working with you in the future.

I will be pleased to answer any questions you may have. Thank you.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

It is with great pleasure that I welcome this Fourth Annual Spring Conference of the Association of Teachers of Preventive Medicine to the National Institutes of Health.

Your timing is excellent, in view of the major emphasis on the role of research in health promotion and disease prevention in our government and among our people. This Administration places the highest priority on disease prevention which has always been a major objective of biomedical research. The NIH view was well stated by Donald Fredrickson, my predecessor as NIH Director, when he said:

> "Our product is knowledge—fundamental knowledge--knowledge about life, disease, and malfunction. And our ultimate aim, the aim of all research, is prevention, because that clearly is the most useful extension of knowledge in the field of health."

As for the Department, Secretary Schweiker said at his nomination hearings that he would "like to be remembered as the Secretary who put preventive health care at the very top of the medical agenda." He reaffirmed that view here at NIH last October in a symposium attended by some of you.

The Secretary said that "research done at the National Institutes of Health will help us guide our prevention strategies into the 80s and beyond. Even in a period of fiscal restraint, this investment has my strong support, because through it we are able to expand our knowledge and then apply it to the day-to-day practice of preventive medicine."

The Assistant Secretary for Health, Dr. Brandt, has pursued the prevention emphasis in his NIH program and policy planning sessions. And the Administration underscored its support for research in proposing an increase for NIH in the President's budget submitted to Congress.

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*Presented at the Fourth Annual Spring Conference of the Association of Teachers of Preventive Medicine in Masur Auditorium on April 22, 1982.

**Director-Designate, National Institutes of Health.

As teachers of preventive medicine, you have a difficult but extremely important role in this initiative. I don't envy you your task as you seek to influence intractable human nature. Everyone knows that an ounce of prevention is worth a pound of cure . . . and yet we hear from the recent report of the Surgeon General that cigarette smoking is still the single, most important preventable cause of premature illness and death in the United States.

The behavioral issues in disease prevention are indeed knotty and complex, as are the puzzles in biomedical research. I can assure you that we are your partners in this endeavor and that we are working hard to provide you with knowledge and technology that will facilitate your disease prevention efforts. Through you and your students, biomedical findings can be incorporated into medical practice for the benefit of all.

This is a propitious time for biomedical research related to disease prevention because the "biological revolution" is providing a rapidly expanding knowledge base that promises to unlock the mysteries of many diseases. We have moved a long way toward understanding diseases caused by genetic defects and how some of these can be prevented. The incidence of stroke has dramatically decreased during the past decade and myocardial infarction is less frequent. Recombinant DNA technology has made possible the production of in vitro insulin and growth hormones. Hybridoma technology is opening up better diagnostic testing and offers promise in therapy of cancer and some infections.

Despite such achievements, Secretary Schweiker noted last fall that the long-standing role of NIH in research related to disease prevention is neither well known nor fully understood in Congress and in the Department itself. He challenged us to better inform decision-makers and the public of our efforts and accomplishments.

The Directors of the NIH Bureaus, Institutes, and Divisions agreed that we could well take a hard look at prevention-related research and place greater emphasis on such work. In those discussions, it was decided to appoint a coordinator to implement an NIH-wide initiative. The task was assigned to Dr. John Seal as Special Assistant to the Director for NIH for Research Related to Disease Prevention. He follows me on this program.

Our primary objective is to engage universities, medical schools, and other health care institutions in the Department's initiative in health promotion and disease prevention. You and your colleagues are an important link in this effort to transfer the benefits of biomedical research to the public through your students. You must also find

ways to integrate your interests and teachings with other clinical departments in the medical school. In this way, all who practice medicine will be able to provide effective leadership to their patients and communities in disease prevention, in addition to their role in the practice of curative medicine.

Dr. Brandt has spoken of a need for partnership in the attempt to achieve wider recognition of the importance of life style in health promotion and disease prevention. You are in a unique position to play an influential role through your contacts in the scientific and medical communities. I hope you will join in this effort.

I know you have a busy program so I will close and let you get on with it. Again, welcome to NIH.

SELECTING PRIORITY AREAS FOR RESEARCH*

by

James B. Wyngaarden, M.D.**

Before addressing the topic of setting priorities in research, I would like to state a few personal tenets concerning research management. The first of these is that the great discoveries in biology and medicine, those that have markedly changed the course of science or have led to major breakthroughs in the management or prevention of disease, have rarely if ever come from program planning by research managers. They have been achieved by individual scientists pursuing new leads as they have appeared, most often during research that was conducted without a specific application in mind; and frequently the creative discovery leads to applications in fields rather distant from that in which the seminal observation was made. A second tenet follows from the first, namely that in setting priorities in fund allocations, it is important to assign the bulk of a large research budget to the support of basic research that is investigator-initiated. Thus from 50 to 70 percent of the budget of the National Institutes of Health is spent in research designed to develop new knowledge in biology and medicine, rather than on targeted objectives. A third principle is that "program management" should be limited to the application of basic knowledge to prevention, diagnosis or treatment of specific diseases; to the transfer of new technologies into medical diagnosis or treatment; to clinical trials of promising agents or interventions; and similar activities.

Within these defined and limited situations, the planning of scientific programs becomes a most challenging responsibility. The problems inherent in any planning effort are exacerbated when the data base is difficult to determine accurately, when it is necessary to assign priorities among equally important goals because of limited resources, and when changes in fiscal realities impinge upon planning for long-range objectives.

The selection of priority areas for applied research depends on assessments of:

- the physical, emotional, societal and fiscal burdens of various diseases;

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* Presented at the Pan American Conference on Health Research Policies in Caracas, Venezuela, on Tuesday, April 27, 1982.

** Director-Designate, National Institutes of Health, Bethesda, Maryland.

- o the readiness of the state of knowledge for application to disease prevention or treatment;
- o the potential impact of various research strategies on reducing the burdens of disease.

ASSESSING THE BURDENS OF DISEASE

The problems of obtaining reliable data on incidence, prevalence, morbidity and mortality of a given disease are too well known to require elaboration. Even when long-term, costly epidemiologic surveys are undertaken, the complexities of research design make it difficult to obtain unequivocal interpretations. Compounding this problem is the difficulty of comparing diseases with regard to their impact on national and international health. The research program planner must depend on his or her "clinical impressions" and professional judgment as well as the impressions and judgments of other experts. The data, even when unequivocal, are more likely to provide clues than definitive answers to the question of which disease should receive high priority in a research program.

The use of assessments of the burden of disease in decision-making about research priorities is complicated because not all factors are quantifiable. It is difficult to compare the burdens of acute vs. chronic diseases; of pediatric vs. geriatric disorders; or of prevalent diseases with low morbidity and mortality vs. relatively rare disease of high morbidity and mortality. Similar difficulties arise when attempting to compare the burden of diseases affecting different age groups where loss of earnings during productive years must be considered, as well as the direct costs of the illness.

For some diseases, notably cancer, cardiovascular and infectious diseases, the impact on national and international health is of such dimensions as to warrant high priority. Other diseases, however, may receive high priority because they provide unique research opportunities despite their relatively low prevalence or limited geographic distribution. These comparatively rare diseases may have well-defined metabolic or genetic characteristics that make it possible to study underlying mechanisms that also occur in more prevalent disease but are masked by complicating changes. An interesting example is Huntington's disease, which is a genetic disorder of low prevalence in the United States. However, the National Institute of Neurological and Communicative Disorders and Stroke has given priority to a study of this disorder in collaboration with scientists at a university in Maracaibo, Venezuela. A population of 200 patients descended from a Spanish sailor who arrived in the country in 1860 is providing a unique

opportunity to study an inherited disease with neurologic manifestations that are similar to those in Parkinson's disease. This is a valuable approach because the neurologic manifestations of the more prevalent Parkinson's are less well-defined than those in Huntington's disease.

ASSESSING THE STATE OF KNOWLEDGE

The hunger for new biomedical knowledge is virtually insatiable. But in assessing the state of knowledge for the purpose of selecting priority areas for research, the assessment must be in the context of the research strategy.

If disease prevention is the goal, the program planner must determine:

- what is known about the etiology and pathogenesis of the disease;
- whether the causal agents can be reduced or eliminated;
- whether interventions are known that will prevent the progressive changes that result in symptomatic disease.

If disease management is the goal, the program planner must determine:

- whether diagnostic techniques are adequate and whether they can be used in community settings;
- whether therapeutic measures have been validated in clinical trials and whether they can be used in community settings.

In setting priorities for research that will lead to the acquisition of new knowledge, decisions must take into account the gaps in present knowledge, the need for knowledge that is not yet available, the readiness of the field for further advances, and the cost of various research approaches.

ASSESSING THE IMPACT OF RESEARCH STRATEGIES

Development of Knowledge through Basic Research

Beyond the realm of "program management" in setting research priorities, but rightfully of high priority in fund allocations, is basic research by the competent investigator who selects his or her own area of inquiry. The health-related contributions of this type of investigation have been abundantly documented and are well recognized by all levels of program planners for biomedical research. The importance of protecting

this type of investigator-initiated research and of achieving stability in a period of contracting resources is the subject of Dr. Donald S. Fredrickson's paper, "Biomedical Research in the 1980s," that you received and needs no amplification here. As previously mentioned, the most innovative research and most important scientific breakthroughs have been achieved by the individual scientists pursuing new leads as they appeared.

Disease Prevention

There is virtually a consensus among planners and managers of research programs that major improvements in national and international health will result from preventing diseases rather than from treating them after they occur. Recent examples are poliomyelitis, smallpox and measles. Another that may soon be added to this list is hepatitis B. Many of the diseases that are leading causes of mortality today are a consequence of such controllable factors as environmental contaminants, personal habits or life-styles (for example, cigarette smoking, and poor nutrition). In establishing research priorities, the cost effectiveness of preventive measures must be assessed in the context of the fiscal as well as other burdens resulting from the disease.

ASSIGNING PRIORITIES TO AREAS FOR RESEARCH

It is difficult to overstate the complexity of this process, because in so many instances there are dichotomies for which cogent arguments can be made for either alternative. Examples are:

- Investigator-initiated vs. mission-oriented research. The value of the former is well accepted, but when important questions about disease are not being addressed the program planner must correct the imbalance.
- Prevention vs. treatment of disease. The thrust toward preventive studies today must not obscure the need to improve the management of nonpreventable diseases or to treat those persons who have acquired preventable disorders.
- Basic vs. applied research. There is no lack of advocates for basic research and no dearth of evidence of its value, but this should not obviate the need for technology transfer and the development of new approaches to improved diagnosis and therapy.

The program planner who must select priority areas for research has an awesome task, a task requiring knowledge of disease problems and their impact, of what has been achieved in fundamental and applied research, of what is ready for transfer from academic to community settings and what must be done before such transfer can be

achieved. In making decisions the planner must be sensitive to the needs of many constituencies in the biomedical community as well as to national and international health needs. And the many factors that enter into a decision must be weighed against the availability of resources and the fairness of their utilization.

Although one cannot plan a discovery, one can attempt to identify, through sufficient expert input, those scientific areas likely to yield beneficial results over the short run.

Plans must, however, be flexible and able to accommodate to the unexpected. Thus, a plan is not an absolute blueprint, but it does establish goals and objectives toward which scientific workers can strive, and can aid in the assignment of priorities for the optimum use of research resources.

REMARKS*

by

James B. Wyngaarden, M.D.**

Thank you, Dr. Kupfer. I am pleased to be here to share in this announcement of results from a National Eye Institute clinical trial -- particularly when the findings are as favorable as these. I understand that this study's results may save more than a million Americans from severe visual loss over the next decade, and save as much as $2.5 billion in tax monies as well. So, for both humanitarian and fiscal reasons, I'd like to thank everyone involved in this study. That would include you, Dr. Kupfer, and members of your staff who envisioned the need for such a study; it would include the scientists who designed it and carried it out; and, of course, the patients who agreed to participate in the study, knowing that it would advance medical science but would not necessarily benefit them personally. You can all be proud of this effort. I, too, am proud, because your success has given me a wonderful opportunity: at the very outset of my tenure in the NIH Directorship, I am able to stand up before an audience of reporters and say, "Here is good news from a Federal agency — an agency that is doing exactly what the taxpayers want it to do, and repaying their investment several times over." It is a pleasure to say that. And I expect that, given the productivity of NEI and the other Institutes here, I'll be saying it on many occasions in the future.

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* Presented at the Senile Macular Degeneration Study news conference at the Lister Hill Auditorium on May 6, 1982.

** Director, National Institutes of Health, Bethesda, Maryland.

MEDIA BRIEFING

James B. Wyngaarden, M.D.
NIH Director
National Institutes of Health
Bethesda, Maryland

May 11, 1982

Introduction by Storm Whaley: We are happy you are here, and I am sure you will want to ask Dr. Wyngaarden some questions. This is strictly a get-acquainted session. Because it is that, he will not have a formal statement but will be interested in what you are interested in and your questions. I would ask that you identify yourself and your medium just for Dr. Wyngaarden's benefit, because undoubtedly he'll be seeing more of you as time goes on. It's now my pleasure to present the twelfth director of the National Institutes of Health, Dr. James Wyngaarden.

Dr. Wyngaarden: Storm, thank you very much, and welcome to all of you. I think I've met many of you by telephone during the early days of fall when my name first surfaced - - when I was advised not to say too much and advised to wait until confirmation had taken place. As I think most of you know, that did occur a week ago Friday in the office of the Assistant Secretary and suddenly this idyllic period of all privilege and no responsibility has come to an end. I now have to not only sign my name but be responsible for what's written above it.

I'm delighted to see all of you and would be very pleased to get to know you this morning and in the days and weeks ahead

and be delighted to meet with you on whatever occasions you might like. This morning, as Mr. Whaley said, we scheduled this get-acquainted session and I'd be glad to respond to any questions that you might have.

Before doing so, I want particularly to pay tribute to the staff at the NIH and especially Tom Malone and Ed Rall, who have really carried the responsibilities of the Director's office for nearly a year now and in a magnificent way, and in addition have spent countless hours in my education in getting acquainted with this position. I have developed an even greater respect for them than I already had on arrival. I am happy to say that they will continue in the institution and look forward to that association also.

So we'll just turn it open to anyone who might like to start it off.

Q: A number of the institutes are without permanent heads right now. When can we expect to have some of them filled?

Dr. W: Several of the search committees have reported, and I was given the green light to interview those individuals on the lists who were in the Public Health Service or in the Department. I have done that. That includes the Neurology Institute, as I will call it, the Heart Institute, the Child

Health Institute and the OMAR vacancy - - Office for Medical Applications of Research. Almost all of us also have candidates on the "short list" who are from outside the NIH. We have now scheduled interviews with all of those - - mostly in May, although a few do extend into early June. I would expect that relatively soon thereafter we will have some decisions.

Q: [Questioner asks that Dr. Wyngaarden run through a list of the vacancies. Another asks that the question be repeated.]

Dr. W: The question was which institutes have vacancies. They include the Neurology Institute, the Heart Institute, Child Health and Human Development, the Arthritis Institute. The search committee has not yet reported [on the last of those] The Dental Institute has not reported. The Aging Institute will become vacant in the late summer when Dr. Butler leaves, and a search committee has been identified and is in the appointing stage at present. And then there are some other key vacancies in the division areas - - Division of Research Resources, the OMAR I mentioned, the Office of Program Planning and Evaluation, the Deputy Director for Science. Those are the key ones; I may have missed one or two.

Incidently, Dr. Fredrickson has told me that he had about the same number of vacancies when he took over, so I think there's nothing unique about this situation. There's a

certain periodicity to some of these appointments. We have somewhat more at this exact moment than we might have had if the directorship had not been vacant, because some of the committees actually were prepared to report a number of months ago, and the reports were held for my arrival. So there's been a stockpiling of a couple as well.

Q: Do you have any "marching orders" from the administration for any priorities for programs here?

Dr. W: No. I'm aware of certain special interests that the Secretary has and that previous Secretaries have had - - in prevention, for example - - but no marching orders.

Q: Do you have any blueprints for changes that you have in mind?

Dr. W: I think the response that I would have to that is that in a period of budgetary uncertainity and obviously constrained budget - - whatever it turns out to be - - the highest priority on my agenda would be to continue to emphasize those aspects of NIH activity that I think have proved so extraordinarily valuable over many decades. In my view, that rests fundamentally on the support of basic biomedical science with a high priority given to the investigator-initiated

grant mechanism. At present about 50% of the NIH budget is in that category. It had been at about that level some years in the past, and then over five or six or seven years ago that category had become considerably smaller, as you know, with contracts and centers occupying a larger percentage. That has moved back toward a figure I just indicated and I would hope to keep it there, because I believe that's the bedrock upom which the whole system rests and thrives.

The second very high priority, which is really closely linked with that, is that of training. I think we have to continue to produce outstanding scientists through the university mechanisms, fundamentally - - training grants and fellowships. Those two, of course - - two categories of new grants and training starts - - occupy a very large percentage of the stabilization policy that I fundamentally agree with. I think the figures are perhaps not so important as the concept - - that we try to maintain a fairly stable approach to the funding of research grants and to the start of traineeships. In a period of some instability, those two emphases have done more to stabilize and encourage young people coming into the system than all others. I think they participate in the centers and in the contract mechanisms and clinical trial mechanisims. But fundamentally, it is the presence of some reasonable assurance of new starts and

continuing training positions that stabilize the system and will continue to attract the best of young people into science. So I intend to emphasize those--those are obviously fields that don't have the same kind of constituentcy as some others, but I think that they have and should continue to receive a very high priority.

Q: I think that some of the research community does not feel that there is that kind of stabilization at present. Could you go over for us the numbers again in terms of numbers of grants over the last couple of years?

Dr. W: I think stability as a concept was emphasized as a way of reducing the oscillations of the system. When one looks over the past decade, the number of new starts has ranged from--I think as low as around 2,900 to 3,000 to as high as 5,800 or 5,900 but somewhat unpredictably. Under Dr. Fredrickson, the stabilization goal was to achieve something like 5,000 new starts per year. That was certainly not intended as a ceiling, and I would tend to look on it as ideally a floor, but in the presence of a constrained budget, obviously we have to operate at somewhat less than that. But as the economy recovers, I would hope that that could be a target that we could keep in front of us. On the training side, the numbers that the NIH has dealt with in recent years have essentially been the

recommendations of the Academy Committee on Biomedical and Behavoral Research Personnel. The number of traineeships and fellowships, in the NIH component of that recommendation, is 10,750 per year. We have been about 1,000 below that in the current year. In the President's projected '83 budget (not passed of course), those numbers would be about 4,100 new starts, and about 8,900 traineeships.

Q: What about the question of whether or not that 4,100 new starts is a real figure? Wasn't that figure arrived at by coming up with new formulas?

Dr. W: That's correct. That figure assumes some other adjustments in the '83 budget. One of those is to reduce the amount of the non-competing renewals by three to four percent. Another is to reduce the amount of institutional support attached to the traineeships and fellowships by about fifty percent and to reduce the indirect cost payment by ten percent. Those three adjustments would make possible 4,100 new starts and 8,900 traineeships.

Q: [Questioner asks what would be the effect if there were no compensatory changes.]

Dr. W: The number of new starts would be around 3,100 or 3,200, I believe. I'm not saying that precisely but in that range.

Q: Are these figures that you've cited consistent with the goal of stability?

Dr. W: Given the economy, they're as close as we can come. I think the decision--or the proposal, as it's yet not a firm decision--to approach the '83 budget along the lines I've indicated is some attempt to distribute the pain, because there's some pain in this. But it has adjusted the decrement in the budget to affect the new starts, the continuing obligations, the traineeships, and the institutional allowances in what was considered to be a fairly balanced manner. We've obviously not pleased everyone with those suggestions.

Q: [Questioner asks whether universities have a legitimate complaint or whether they are just asking for everything they can get.]

Dr. W: I don't think the latter. I think the universities are in a very difficult spot. I've spent a fair amount of my life in that arena and have an appreciation for the financial problems of institutions. They are hit as everyone else is by the increasing cost of inflation and in addition to that the reduction of funds for student allowances. The adjustments of Medicare and Medicaid reimbursement have placed great strains, particularly on the academic health centers.

Not surprisingly, the universities are concerned about the suggested reduction in indirect cost reimbursement.

The other side of that of course is that's been a rapidly growing category. The indirect cost was capped at fifteen percent in the early '60's, and, as a result of the Wooldridge report, the Department began to treat those as true costs and deal with them on an audited basis, as a reimbursement figure. Since that time indirect costs have grown now up to twenty-nine point five.

There are many sub-categories to indirect cost. The largest are space costs and the category called departmental administration. Those occupy almost a third of the indirect cost category each. The fastest growth single category has been those two and particularly the departmental administration.

Those definitions are arrived at not here at the NIH; that's a departmental decision. I think there will likely be another very careful look at the allowable components of the indirect cost formula in an effort to arrive at some, perhaps, more uniform approach to it, because there are many, many different formulas depending upon the university accounting systems.

There are audited costs, there are true costs of research, and some university administrators feel that the NIH should pay true costs of research even it it means funding for less research. On the other hand, I'm also concerned about the point I made earlier--that is, those factors that attract the

best young people into biomedical science. I think the continued emphasis on a number of new starts and available traineeships are important factors in that. My own observations are that that aspect of the stabilization philosophy did a great deal to stop the slide away from interest in biomedical research--as people said, "Yes, there is a future here."

Q: [Questioner asks whether NIH will reduce the indirect costs charged to grants, thus taking more money out of research projects--that is, indirect costs will be shifted to direct costs.]

Dr. W: It might result in that in the future, but there's a limit to what is apparently permissible. That's an accounting matter that is taken up at the Department level.

Q: On quite another subject, there's been a lot of concern in the scientific community about the fraudulent use of grant money. I know NIH has some plans in that regard on what to do about that problem, and I wonder if you could give us an update on it.

Dr. W: There's no question there have been some regrettable and well-publicized episodes of abuse in this conduct in science. A number of cases have been brought to the attention

of NIH in recent years and in most cases resolved in not too long a period of time. The total number is still a very small fraction of the number of grants that have been in force during that same period of time--certainly less than one per thousand that have come to our attention. There may be others, of course. The number should be zero. Obviously, we don't condone any of this. They're not all of the same degree of seriousness. Some of them are in the nature of technical infractions of informed consent. Some others are undeniably misconduct of the worst kind--frank fraud and faking of research results.

The NIH view is that this is in the first instance an institutional responsibility to investigate. We do expect to be notified when any such event comes to the attention of a project director or university official. It is our responsibility to notify the Inspector General. Usually if it is in an area of--it does involve embezzlement or gross mismanagement of funds--the Inspector General returns it to the NIH to handle. We have within the NIH an alerting system such that all institute directors are now notified when such a case has been alleged against one of our grant holders, so that if there are other grants or contracts in other institutes, they are prepared now to deal with that in a somewhat more systematic manner than in the past. The degree of seriousness obviously dictates what the next step may be. If the institution resolves it and it appears that their handling of it is

satisfactory, it may end there. If not, the NIH can and has appointed investigative committees to conduct their own investigation and report back, and the remedies or strictures that may result from that again are several, which at the most serious may include debarment for a fixed period of time from any access to any further NIH support.

Q: Has that in fact happened? The debarment?

Dr. W: It's my understanding that there's not been any debarment as yet.

Q: [Indecipherable.]

Dr. W: I think there are a couple of serious instances that are still under investigation. What the recommendations on those will be has not been reported officially.

Q: Could you comment about some of the bills that have been floating around to add new institutes to NIH? [Questioner asks about NIOSH and creation of new institutes.]

Dr. W: Yes. Let's take the institute question first. My own view is that, particularly in a period of constrained resources, creation of new institutes seems to be rather illogical. The purpose of advocating the creation of new

institutes is clearly to call to our greater attention to a given area and also presumably to acquire greater funds for that particular area. At present, that could only happen at the expense of some other activity of the NIH--some other institute. And we think that at present there's no need to create additional institutes to meet the objectives and missions of those programs.

With respect to the NIOSH question that you raised: The NIH has a mission which is fundamentally that of supportive research and of the introduction of results of research or other developments into the practice sector but not of actually getting engaged in operations or regulations of the sector itself. NIOSH sits in between the regulatory and research area in having a very large responsibility for setting of standards, which then become the basis for regulatory activities. We think that's not so compatible with the NIH mission and would fit better with that of CDC, and would prefer to see it left there. There is some overlap with the activities of NIOSH and the National Institute of Environmental Health Sciences, but other than that, the NIOSH activities really are fairly well distinct from those of the NIH.

Q: How about the National Center for Health Care Statistics? There was talk about moving that, either into NIH or [?]. Would that be compatible with the NIH function?

Dr. W: That would be of all the ones suggested the most compatible.

There is some logic for its activities articulating effectively with those of the National Library of Medicine. I don't know that a lot would be gained from doing it, but it's perhaps a move that would fit reasonably well.

Q: I wonder if you could comment on plans for the new consensus meeting program. Is that program to be ongoing?

Dr. W: Oh, indeed. There are a half dozen or more consensus conferences in the planning now.

Q: These are going on indefinitely?

Dr. W: Yes. As a matter of fact one of them is being copied and duplicated in Sweden shortly--so successful here, they have decided to follow that lead.

Q: Could you tell us your views on abortion and whether or not you think that subject will come up as you look at possible grants or research?

Dr. W: The NIH has not been active in abortion procedures itself, as you know. A good deal of the research that is financed by the NIH is clearly directed toward prenatal diagnosis, which then forms a basis for a decision. I believe that the abortion decision should be an individual decision. I believe

in the freedom of choice and that the NIH should provide the maximum scientific basis on which intelligent choices can be made.

Q: Do you perceive any changes? You mentioned several things that would be continued. Do you have any new ideas for change in mind?

Dr. W: As I said earlier,I'm a firm believer that the NIH system as it exists is very sound and that we need to protect those things which have been most successful in the past. And they have been very successful. I think that one of the challenges will be to continue to protect the undifferentiated basic science that the NIH has supported so well over the years. Many of the exciting things that are here now--the development of recombinant DNA technology, the number of vaccines that are potentially doable, rest on developments in that field of ten or twenty years ago at a time when we didn't know where restriction endonucleases would lead. And I think that's an area in which the future health of the country depends very heavily. That, of course, is an area that is supported--ninety percent of it in this country--by NIH dollars. I think that's critical to preserve. That must be done at a time when there are more and more interest and activity by groups that have perhaps more restricted interest in mind and are looking at more practical payoffs in a shorter term. I'm not saying for

a minute that that's bad. I think a great deal of the growth of the NIH has been occasioned by testimony from individuals and groups of that sort, but the pendulum has swung rather farther in that direction in recent years. As I commented earlier I think it has swung back now in the last few to a distribution of funding mechanisms that I'm quite comfortable with.

Q: Did you take part in the recent acceptance of the changes in the DNA guidelines that were published?

Dr. W: No. That was before I came aboard.

Q: Do you have any feelings about those guidelines in terms of whether they should be relaxed or be more restrictive? Have you given this any thought whatsoever?

Dr. W: Well, some. I know that the committee that looks to [?] entertain the point of view where they should be dropped altogether. I think a substantial body of responsible scientists have felt that the need for such guidelines may have passed. I think it is wise to continue them in the manner that has been continued for the more immediate future. I don't think there's any need to make them more stringent than they are at present.

Q: To take you back to this subject of abortion. I'm not

sure what you meant by freedom of choice, and I can think of two areas where your opinion at NIH might be involved. One would be this whole attempt to bring science into the legislation on the Hill and the definition of when life begins, and the second would be the question of what you would be doing about in vitro fertilization, which is a question I would like you to comment on also. Again, I am not sure what your position is on abortion.

Dr. W: Well, as you know there have been many attempts recently to draw more stringent legislative restrictions on the use of federal funds for abortion and even to outlaw its performance except in very, very restricted situations, and I was associating myself with a somewhat more lenient point of view--feeling that is a couple's decision to make, not a legislative decision.

Q: Well, what about in vitro fertilization? Now, NIH is really, I forget exactly how it was handled, on a hold on research in this area. Now it is going ahead around the country. We hear reports of this university or that university. What responsibility does NIH have to both monitor this as well as do some research that would be involved with the human aspects in both laboratory studies? There's no one. Whatever happened to Soupart? Can you answer

that one? From Vanderbilt?

Dr. W: I don't know the answer to your last question. I believe this is a legitimate area for biomedical research, and that in vitro fertilization may solve the problem of infertility for certain couples, and, as you know, we are active in that field at the animal level, and I would have no problem with carrying this forward into the human level for a situation such as that.

Q: I don't know exactly where you stand. It's not clear to me. I think there's requests pending. Will you act upon that, or how will that work?

Dr. W: I'm not fully acquainted with that request. It is a matter that is dealt with in the Child Health and Human Development Institute, and I know that this has been put on hold for the present. It's an area that we are trying to discuss more fully, and I've given you a personal point of view. It's not an NIH point of view at the moment.

Q: Well, do you think it's possible that NIH might lift this hold and go forward with some federally funded research?

Dr. W: I would have to discuss that more fully. I can't really answer that question just yet.

Q: In connection with the previous question, you had mentioned

as an outgrowth of recombinant DNA research that potential patentable vaccines. Could you be more specific? Do you know [whether] the ones that exist now will be made in a different way?

Dr. W: What I was referring to there is a general potential for vaccine development, and there are studies of this general kind going on. The ability, for example, to excise a portion of a viral genome--to clone that and use that as a vaccine antigen in such a way that the portion of the genome is itself not infectious. Those techniques rest on the studies that I mentioned of gene structure of restriction endonucleases, the ability to excise a portion that has antigenic potential but not infective potential. That theoretical basis now makes it possible to approach some of the serious viral diseases. For example, Norwalk virus, which is a cause of a great deal of childhood diarrhea and a very serious disease in certain age groups. That potential now exists. But it didn't exist because anyone said, "let's develop a vaccine against Norwalk virus." It developed because of this great body of fundamental scientific knowledge that was developed without a specific application in mind at the time. That was the point I was trying to make there.

Q: Are there vaccines that you perceive in the coming years besides those?

Dr. W: I think we're on the threshold of an era in which it

is now feasible to approach that problem with the Norwalk virus or many others, and yes, I forsee the next decade as one that's filled with marvelous potentialities for such developments.

Q: In the literature recently there's been a good bit of discussion about altering the principles of peer review. Would you like to discuss this?

Dr. W: I think that peer review is one of the brilliant creations, among many, of the Shannon era. It is really the envy of the world. Many other countries are copying it in one way or another. The peer review is much sounder than many of its critics have indicated. For example, the charge of old-boy networks here is really hard to sustain when one realizes that eighty percent of the members of our initial review bodies are first-time members of such groups. In fact, I think there's room for some concern on the other side--that perhaps we don't have enough of the experienced people recycling through some of these groups. That is a tremendous amount of work and people who have done it for one term sometimes are not so willing to do it again.

But I think the principle of peer review is very sound. It has probably operated a little more comfortably in times of affluence than it does in time of a constrained budget. It's very difficult to differentiate between grants that have

priorities of 160 from those that have priority 162, for example, as it comes out of a peer review vote. But I don't think we've figured out a better way to do it yet. I think that a peer review by people who are selected for their scientific credentials--their expertise in that field is an exceedingly important system that I would hope that we can preserve.

Q: [Questioner asks about a potential set-aside for small businesses.]

Dr. W: First of all, not very many small businesses have invested the millions of dollars in establishing the research capability to do the kind of work that NIH has supported. There is now, as you know, no restriction on small businesses coming in for grant support through the usual peer review system. That restriction was lifted for profit-making organizations as recently as January of this year. So we haven't had a chance to see the full impact of that over a sufficient period of time. I think it would be sounder to let that system operate and to see whether some of its problems may not be solved by simply opening the doors to applicants from small business as well as from university communities. The NIH already does have a substantial amount of its budget going to small businesses in one way or another. It is in the range of thirty million dollars a year through one type of contract

or other, so that small businesses have had some NIH dollars flowing into that category. But I think it would be better to allow them to compete through the usual mechanisms. There are some members of small business on review groups, and we would look with favor to enlarging that number and to see whether we can't operate within the well-established mechanisms rather than through a set-aside.

Q: [Unintelligible]

Dr. W: I would prefer that, but if that's not the way it turns out then obviously we will deal with it in whatever manner Congress dictates. I think we'd like to see the small business set-aside at least put on hold for a time to see how the present system can operate, now that's it's been changed just recently.

Q: The Cancer Institute has a number of organizational budgetary features that set it apart from the other institutes. Do you favor retaining the Presidential Cancer Panel and direct budgetary access to the White House?

Dr. W: I think they've worked well. There were many concerns about those provisions early on. But in actual operation, they have worked well, and we have worked well with the Cancer Institute in budgetary matters as well as others. It functions as a component of the NIH with these special provisions. But

they've not been destructive in any way. So I'm comfortable either way.

Q: [Questioner asks whether Dr. Wyngaarden would want the other institutes to have the same "special provisions."]

Dr. W: Well I know that was suggested. I don't think that would be necessary.

Q: Hasn't the Department taken the position that the budget passed directly to the White House should be eliminated?

Dr. W: Yes.

Q: [Indecipherable question.]

Dr. W: I think it is administratively a little awkward to have one institute with provisions that are different from all others. So the two alternatives in implementing that suggestion are either to eliminate it for one or provide it for all. But I think that at the level of practical problems, there is none. With the present system, it works fine.

Q: So you don't care one way or another?

Dr. W: I have more pressing concerns.

Q: Did the President's Commission recently issue its report on protection of human subjects call for a stronger role for OPRR and just establishing-- or giving NIH the responsibility for agency-wide oversight for protection of human subjects? How do you feel about that? And also, how do you feel about-- where are other rules for protection of human subjects--other categories of research subjects, including children? There's another category of research regulations that were still pending for quite some time, and one of the recommendations was that NIH get on with issuing these regulations.

Dr. W: I'm not sure really that I follow--or am well enough informed with other agencies' involvements in what their differing requirements may be. I think our protection of human subjects-- our regulation of protection of human subjects at the NIH are in pretty good array at the present time

Q: Getting back to peer review, there seems to be some concerns about the compression of priority scores. [The questioner makes undecipherable comment about normalization of priority scores.]

Dr. W: As indicated, when funds get tight and when paying on a very low priority score and paying only twenty-five to perhaps thirty-five or forty percent of approved grants, there is concern whether the system is adequately differentiating among those that should be paid and those that perhaps should not. I think

most institute directors are uncomfortable with the rather low fraction that's being paid whatever the score is, and feel that unless we're paying closer to forty-five or fifty percent of approved grants, we are excluding some very high-quality research from being conducted. We really don't have a good alternative to that at the present time. There's some flexibility--some grants that may be just outside the priority score are sometimes flagged and brought to the attention of the council for special discussion. They look at factors other than priority scores, such as program relevance. Some institutes have set aside a small fraction of the total grant budget, perhaps one percent, for the funding of grants that might be taken out of the exact sequence of priority scores based on their program relevance. I think that's one way of dealing with this grey zone between approval and disapproval.

Q: [Indecipherable]

Dr. W: Yes, yes, that is a matter of discussion, and we have not implemented that as yet. There's several other experimental programs that are under discussion. The fixed obligation grant is another. Those are matters that are the subject of study by the Director's Advisory Council, but at present we have not implemented those.

Q: There's been some question about the value of randomized

clinical trials. In view of the fact that a lot of NIH's grant money supports this type of research, are there any proposals to tighten the requirements?

Dr. W: As you may know, because of the shortage of funds, no full-scale clinical trials have been initiated since 1978. There have been a few pilot studies. In reviewing the budgetary proposals for fiscal '84 which we are now doing, which is in progress, each institute--or most institutes--have listed some clinical trials that they would like to conduct if funds would permit. Some of these appear to be very important ones, and I hope that we can conduct somewhat more than we have. It's true they're very expensive. A great deal of thought is given to the cost of the clinical trial and the trade-offs that are involved. We support a clinical trial at a certain number of dollars. It means that that eliminates X number of investigator-initiated grants at an average cost of, say, a hundred thousand plus. Each institute director on the staff weighs those factors very heavily. I think the emphasis on the stabilization philosophy of the last few years has in part reduced the number of clinical trials that were initiated. They are large; they are complex; they're expensive; they take a long time. When one initiates them, one commits funds for a number of years in the future. For those reasons, not very many have been done. But I think some should be done. There are excellent ideas that have been suggested, and I hope we can do somewhat more.

Q: [Questioner asks what areas they might be done in.]

Dr. W: There are some in the cancer field; there are some in the cardiovascular area; there are some in the arthritis field of remedies that are being used--we really don't know whether they're beneficial or not, or whether if beneficial, the risks are being adequately evaluated. Large multi-center coordinated clinical trials sometimes are the only way one can get at that. Clinical trials have proved certain practices to be of value. They've also proved certain others to be of no value and in turn have saved a great deal of money in some instances--more than the cost of the trial.

Q: You would be in favor of starting them up again?

Dr. W: If we can afford it, yes, indeed.

Q: [Indecipherable.]

Dr. W: Yes.

Q: Could you elaborate on the plan or strategy that you might have for implementing this?

Dr. W: Well, there is a department-side coordinated effort in the field of prevention and health promotion in which all of the

agencies of the Department of Health and Human Services are participating. Each has been assigned its primary area of emphasis. At the NIH, ours is chiefly that in research that leads to better prevention of disease and the area of transfer technology, if you will--making certain that those things which are possible to be incorporated into the practice of medicine are facilitated. The CDC has its set of assignments, if you will, in this prevention initiative. This is in the stages of development. I think there will be some announcements on other aspects of the program in a relatively near future from the Secretary's office.

Q: I understand that a number of people were approached about that position of director and turned it down for various reasons. You had a very good position--well thought of in the community. Why would you give up that?

Dr. W: I didn't know that anybody had turned it down, but I suppose it's possible. I thought it was a job of great importance, an enormous challenge. I've always been interested in the interaction of science and public service. I thought, having been a chairman for seventeen years--fifteen at Duke--that it would be enormously stimulating for me to change. Others have persuaded me that the diverse background that I've had, without necessarily planning it in that way, offered some of the qualifications that this job should have, such as a background in science and in education and a member of the intramural staff at one time and a

great deal of contact with extramural activities, with a gathering committee advising the NIH on training. Initially when I was approached I said no, as I had almost everything else. Little by little, I warmed to the idea and when finally asked for a CV, I said, "Well why not?" This is what happened.

Q: Were you given assurances that this position would stay essentially apolitical. There was a long discussion about this years ago, and the NIH director was isolated from politics. Were you given assurances that this will continue?

Dr. W: No, and I didn't ask for any. I think that the relation of the NIH to the administration in the last number of years has been very much of an apolitical nature. Dr. Fredrickson was appointed by a Republican president--continued through a Democratic administration--could have stayed on indefinitely in this one, as far as I know. My having happened to be a Democrat in North Carolina was not an issue.

Q: Did they ever ask about that?

Dr. W: Oh, yes. They just wanted to be sure I hadn't been too active.

Mr. Whaley: I think we're getting personal now.

Q: I was just wondering--There have been accusations that the

Secretary of Agriculture has intervened in the peer-review system. What do you think of that?

Dr. W: I don't know anything about the Secretary of Agriculture intervening in the peer-review system. Sorry.

Mr. Whaley: Thank you Dr. Wyngaarden, very much.

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JULIA MARY JONES MEMORIAL LECTURE*

by

James B. Wyngaarden, M.D.**

I am honored, indeed, to be a participant in this Opening Session of the 1982 Annual Meeting of the American Lung Association and to add my tribute to the memory of Julia Mary Jones in whose name this keynote address is given each year.

I regard this as a challenging assignment. My predecessors as Julia Jones Lecturers have been distinguished leaders in public health, government, and academia who set a very high standard with their addresses. In addition, to one such as I who has devoted a substantial number of years to medical education, the career of Julia Jones represents the highest attainment--her influence lives on through the students and colleagues whose creative interests she stimulated and who carry on her work.

At the time the Trudeau Medal for 1973 was awarded posthumously to Dr. Jones, her many notable contributions to our knowledge of respiratory disease and its treatment were recounted. I found especially appealing one thing said of her as a person--"Her example of excellence and insistence on candor, her disarming informality, her exquisite sensitivity to patients and young doctors and her inspiring humility are qualities that stand out in the minds of her students and associates."

I ask your indulgence when I state with some pride as a recent faculty member that Julia Jones was a graduate of the Duke University School of Medicine.

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*Presented at the Annual Meeting of the American Lung Association, Los Angeles, California, May 16, 1982

**Director, National Institutes of Health

During April and much of March this year, I have been immersed in a process much like preparing for final exams. In this case, the goal was not graduation, however, but matriculation. Once nominated for the post of Director, National Institutes of Health, it was necessary for me to gain approval of a formidable admissions committee, the United States Senate. Obviously, I wanted to be as well prepared as possible for the confirmation hearings and, in the process, to be brought up to speed as nearly as possible on the current complex of issues and opportunities with which the Director of NIH must be concerned.

The briefings have been extensive, ranging over the whole surprising spectrum of matters that have an effect on the ability of the NIH to carry out its vital mission. With the members of the NIH Staff, I have discussed at length the patterns of productive relationships that exist between the agency and its varied constituencies.

From the beginning of the modern era of NIH's history, voluntary agencies like the American Lung Association have joined with us in common cause against disease and disability. Though our roles and approaches necessarily are different, our goals converge. The results of Federal efforts and of voluntary efforts are mutually reinforcing--truly synergistic--so that the total effect is greater than the sum of the parts.

Prior to World War II, the role of the American Government in medical education and in biomedical research was minimal. Private foundations, voluntary organizations, and professional societies were the dominant sources of support and influence in shaping medical education, funding research, and carrying out health promotion programs. Your organization was then, as it is now, a powerful force for improving the health of the American people. When, out of the wartime experience, it was recognized that Federal support of research was not only appropriate but essential, agencies like the NIH were provided comparatively massive support. There were those who predicted that private

efforts would no longer be needed and that support for voluntary agencies would dry up. But one of the remarkable things about voluntarism in the health field has been that it has retained its great strength over the years simultaneously with the rapid growth of large federally supported programs which would have appeared to compete with or wholly supplant the need for such citizen efforts.

That so many of you are here today, representing the thousands upon thousands of volunteers in your local organizations, is remarkable testimony to the vitality of voluntarism and the fact that individuals will continue to give their time, money, and effort to the support of activities in parallel with the Federal Government. The question might be asked: Why do you continue in work that you might well leave to the Government? You know the answers. One is the individual need of the American people for involvement in worthwhile activity--a personal and profound attachment to the purposes of organizations like this one. You know that however adequate the Federal budget might be for the fight against pulmonary disease, such programs would be far short of complete without the widespread and dedicated efforts of volunteers.

Another element in the vitality of voluntarism is the flexibility with which organizations like yours can use their resources to attack obvious problems. The support you receive comes from persons who are committed to your objectives. The support of Federal agencies, through taxation, is not exactly voluntary, and responsible public stewardship demands that we demonstrate to those who may not have great interest in a particular effort of ours that we have used their funds with care and prudence. Research, by definition, is an uncertain enterprise. One of the critical responsibilities of the National Institutes of Health is to select from thousands of good proposals those projects having the greatest promise. We constantly must balance the need for caution in the investment of public funds with the realization that the greatest payoffs may be at the frontiers of research where uncertainty is also the greatest.

The sheer volume of our activity makes it very difficult for us to judge the merit of any substantial number of relatively small research proposals. Among these are many of the exceedingly important first projects that can launch the careers of young investigators. This essential function you perform very well.

There is another reason that makes the American Lung Association and organizations like it key elements in the fight against disease. It has become apparent in dealing with many chronic diseases that individual life styles and habits are decisive factors in the struggle against disease.

New programs of health promotion are being launched by the Government, particularly the Department of Health and Human Services, but we have much to learn, and whatever is done will not supplant efforts like those of the American Lung Association which has a long and distinguished history of successful public education. The need for your efforts and the expertise you have gained through successful experience in health education is greater than ever before.

While most of NIH's interaction with the pulmonary community takes the form of research support, I was pleased to learn of a current collaborative NIH-ALA project in the area of health education. It is an effort to demonstrate the effectiveness of a comprehensive quit smoking campaign. The program, which is being tested in Minnesota this month, involves the use of local television and local ALA chapters. The program package includes filmed segments and scripts for airing during TV news for five successive days complemented by ALA's self-help quit smoking materials and a smoking cessation clinic to follow the week-long broadcasts. We will be evaluating this collaborative effort in a number of cities. If it proves to be of value, it will become another anti-smoking weapon in the ALA arsenal, one developed together by a public agency and a private voluntary organization--a small illustration that public/private resources can be effectively merged to combat a common problem.

Let me turn to an area of mutual concern where the Federal role is critical and, to a degree, unique. I am speaking of basic research--undifferentiated and fundamental studies whose outcome is unpredictable. At the time such studies are undertaken, the investigators frequently do not know in what category of disease the results might prove to be useful. The search for basic knowledge often leads the scientist into strange terrain far from the expected trail.

Since voluntary organizations usually have a high level of commitment to a particular disease or family of diseases, it is only natural that the research emphasis tends to be a few steps removed from basic investigation. This focus on categories of disease is reflected in the structure of the NIH. The names of most of our constituent Institutes are tangible expressions of public conerns about specific ailments. The Congress and the Administration have responded to such concerns by establishing the categorical Institutes and providing funding for their programs.

So we have the somewhat paradoxical situation of the National Institutes of Health composed of units whose names make up a formidable roster of diseases. There is an apocryphal story told around the NIH that when one of our Congressional champions was first told of the name of the National Institute of General Medical Sciences, he objected because, "No one ever died of general medical sciences."

Basic research, as such, has no natural constituency like cancer or heart disease or stroke or lung disease, but our nation has been fortunate that leaders within the Administration and the Congress have recognized that fundamental research is critical to progress in the diagnosis, prevention, or treatment of any and all diseases.

It is important that voluntary agencies concerned about specific diseases carry the message to the public about basic research as well and not leave the responsibility to research scientists alone--who are not always effective spokesmen and who suffer from the appearance of selfishness when they proclaim the importance of the work they do.

In a logical division of labor, the responsibility for conduct and support of basic biomedical research falls largely on the Federal Government. Early this year, the President's science advisor, Dr. George Keyworth, identified such a Federal role in all of the areas of science. Speaking at the Annual Meeting of the American Association for the Advancement of Science, he said, "Arguments for a Government role in civilian research and development necessarily apply most strongly to basic research. Basic research warrants Government support because it is an investment in the future—in a better quality of life, better security, a better economy, and simply better understanding. While basic research should be supported by the private sector whenever possible, Government is responsible for ensuring that the support of fundamental research is adequate . . . Government support of basic research to the extent that such research is carried out in educational institutions influences our ability to meet future scientific and technological manpower requirements."

In a moment I will outline to you some of the current activities and plans of the NIH in the area of pulmonary disease. Before doing so, however, I wish to add a historical footnote which I believe to be timely. This year, your organization is taking the lead in celebrating the centennial of an event of great significance in medicine. The announcement in 1882 by Dr. Robert Koch of the discovery of the Tubercle bacillus was also a landmark in human history. Four years after that announcement, one of Koch's pupils, Dr. Joseph James Kinyoun, became the founding director of the first United States Public Health Research Center at the Marine Hospital on Staten Island. This laboratory, built on the work of Koch and Pasteur, eventually became the National Institutes of Health. I do not believe it presumptuous to say that 96 years and 11 Directors later, the NIH as a kind of lineal descendant of Koch's laboratory continues to reflect the spirit of dedication and scientific inquiry that motivated the European giants a century ago.

As you well know, the NIH is not the only Federal agency involved in pulmonary studies. Some 12 Federal agencies conduct and support such research. Within the National Institutes of Health, 10 of the 11 constituent Institutes have important programs on aspects of lung disease.

Some of the research supported by our Institutes is important to other agencies which have enforcement responsibilities, particularly in the area of environmental health.

The National Institute of Environmental Health Sciences is funding an important study of the effects of both indoor and outdoor air pollution on the health of children and adults. Researchers at the Harvard School of Public Health are studying six cities, each with a different mix of air pollutants. For example, one city has virtually clean air, one city has a heavy concentration of sulfates but no nitrates, another is heavy in nitrates and has few sulfates, and so on. We are studying the health records of a random sample of children and adults to determine whether there is a correlation between particular types and levels of air pollution and specific health effects.

This is the seventh year of data collection, and during that period there has been a marked improvement in data collection and air monitoring capabilities.

These studies are taking place during a time when there has been rising public interest in the health problems that can be caused by air pollution. The ALA's interest in clean air is evident and widely known. The National Observance of Clean Air Week, which fell this year May 2-9, is an annual reminder instituted largely by the ALA.

A significant step was taken at the NIH just over 12 years ago with the establishment of the Division of Lung Diseases within the National Heart Institute, now the National Heart, Lung, and Blood Institute. Since that time, the Division has grown and it now is the dominant Federal entity involved with pulmonary research.

(SLIDE 1) "Lung Research Funding by Federal Agencies

The budget of the Division has quadrupled from $20 million in fiscal year 1971 to its present level of $81 million.

(SLIDE 2) "The Obligations of the DLD" - Budget History

Paralleling this increase in funds, the number of active grant and contract awards has also increased almost fourfold. This expansion has been accomplished by a broadening of the areas of research under investigation by DLD-supported scientists, as well as a redirection of emphasis to new, more promising research approaches. In the past, a major obstacle to advances in pulmonary research was the failure of basic scientists to perceive the relevance of their disciplines to lung diseases, or to draw upon special features of the lung that could further their basic investigations. To correct this deficiency, the Division has used a variety of approaches to help basic scientists understand lung diseases and to encourage work on pulmonary problems. By including researchers from fundamental disciplines in its sponsored workshops, and by issuing requests for grant applications and contract proposals, the Division has reached investigators not previously concerned with diseases of the lung.

In terms of the Division's budget distribution, fundamental investigations of lung structure and function is a leading component.

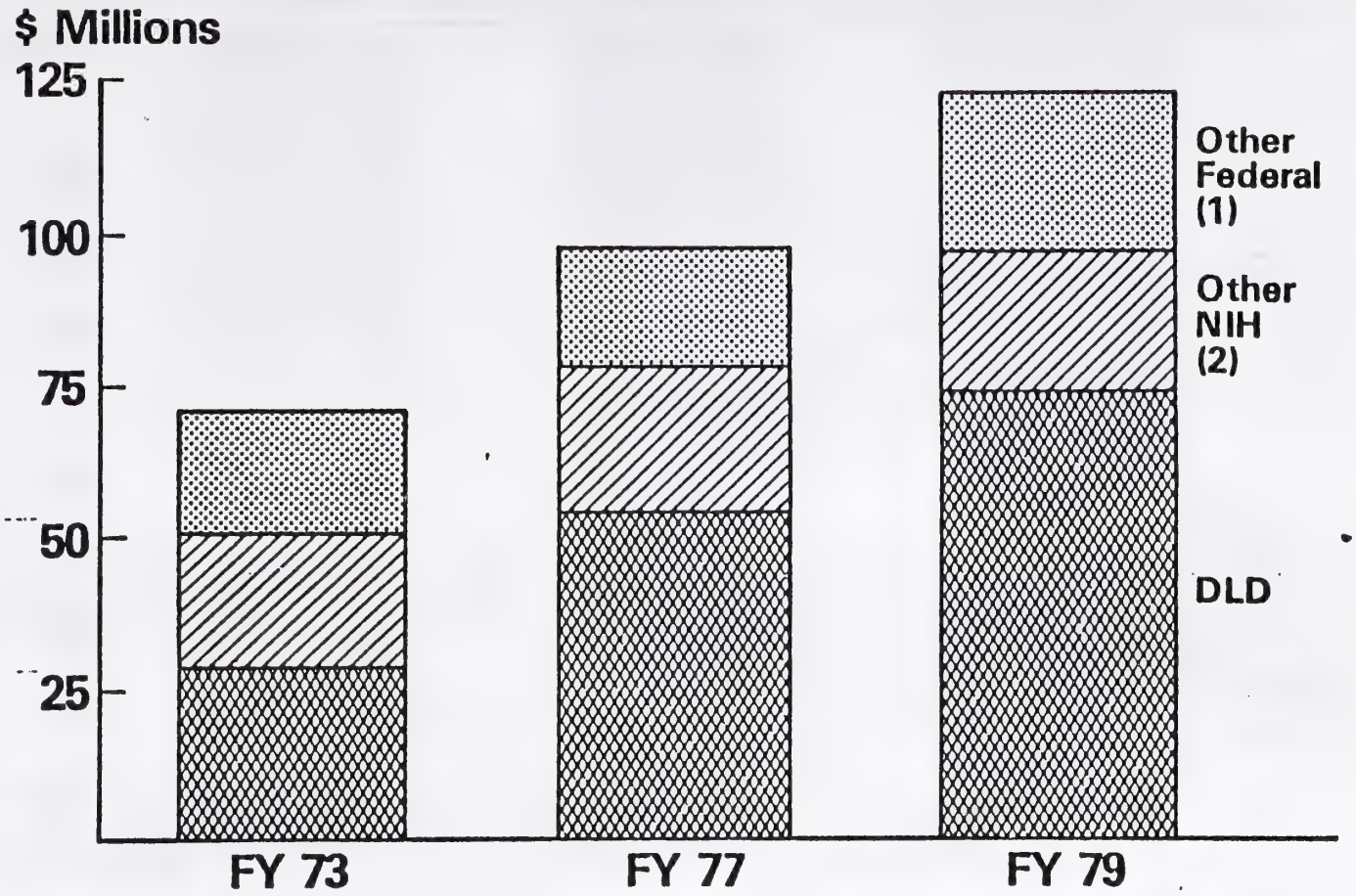
(SLIDE 3) "National Plan Categories"

Research supported through the Structure and Function Program has become a continuous source of knowledge that often becomes the groundwork for programs in diagnosis, treatment, or prevention of specific pulmonary disease. Such programs frequently proceed to the point where the research becomes a responsibility of one of the Division's disease-oriented programs.

Slide 1

One of these or both?

Lung Research Funding by Federal Agencies



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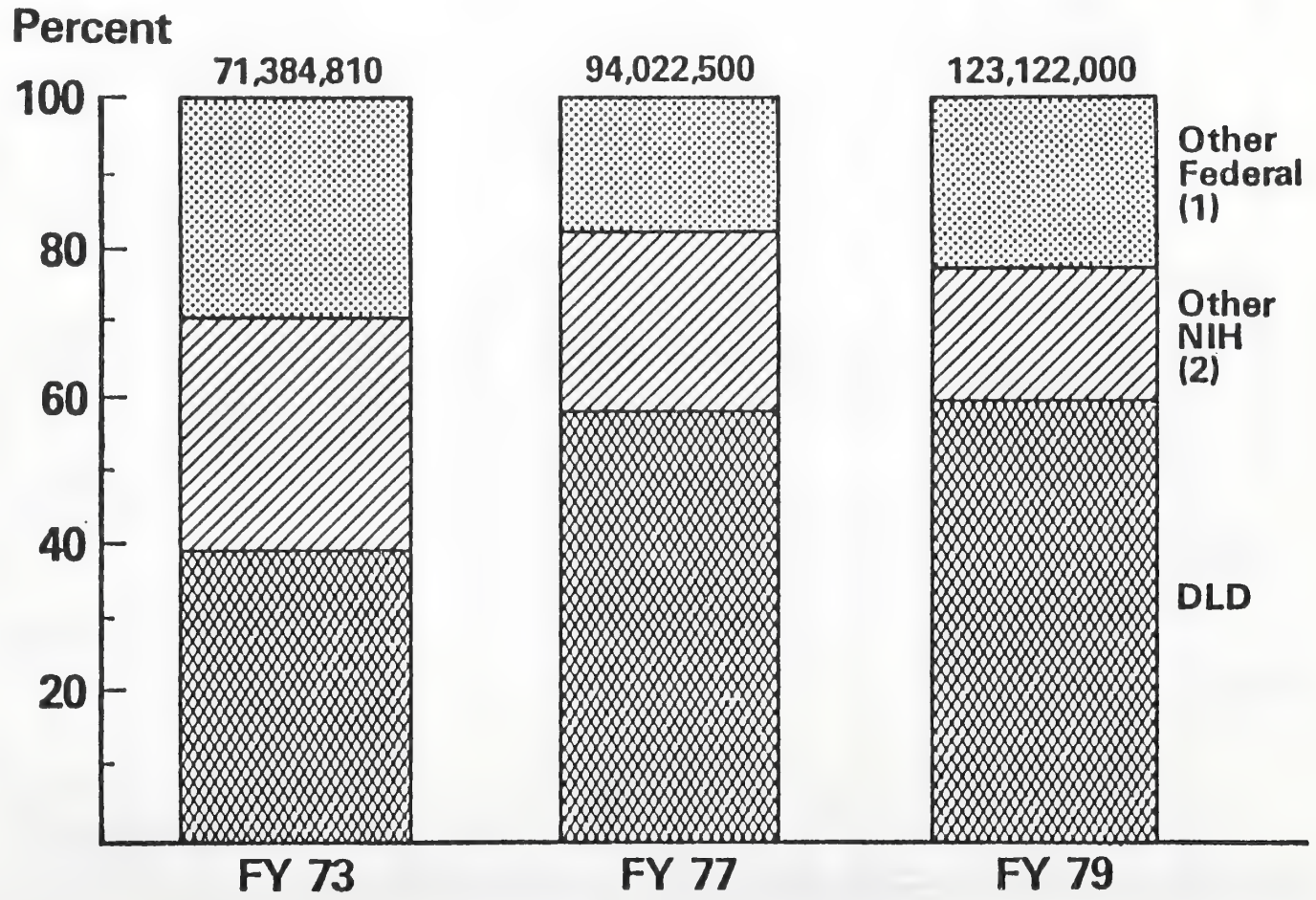
(2) Does not include NCI

Slide I.a

Lung Research Funding by Federal Agencies

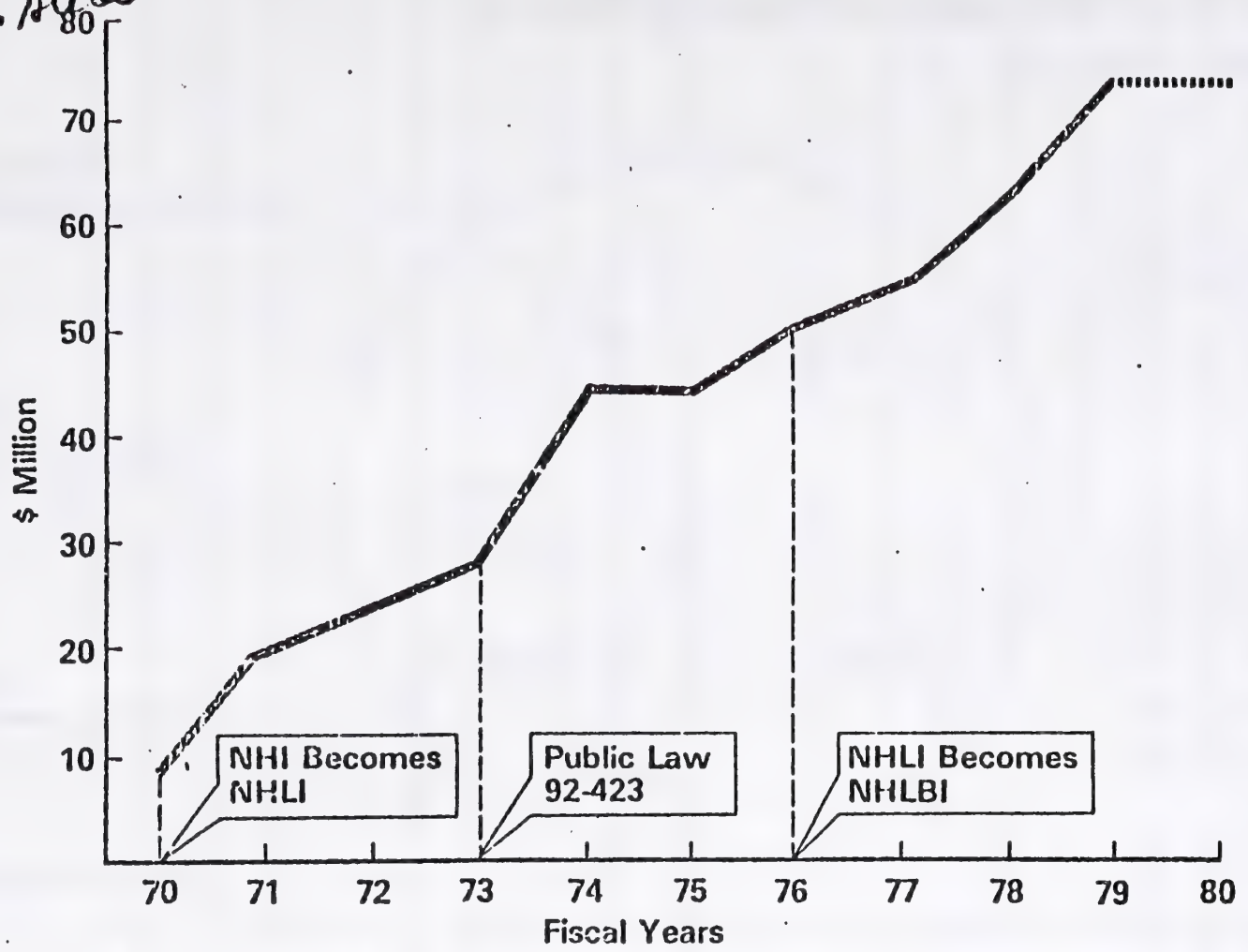


(1) Does not include VA and USDA

(2) Does not include NCI

I'll have an updated version of this slide

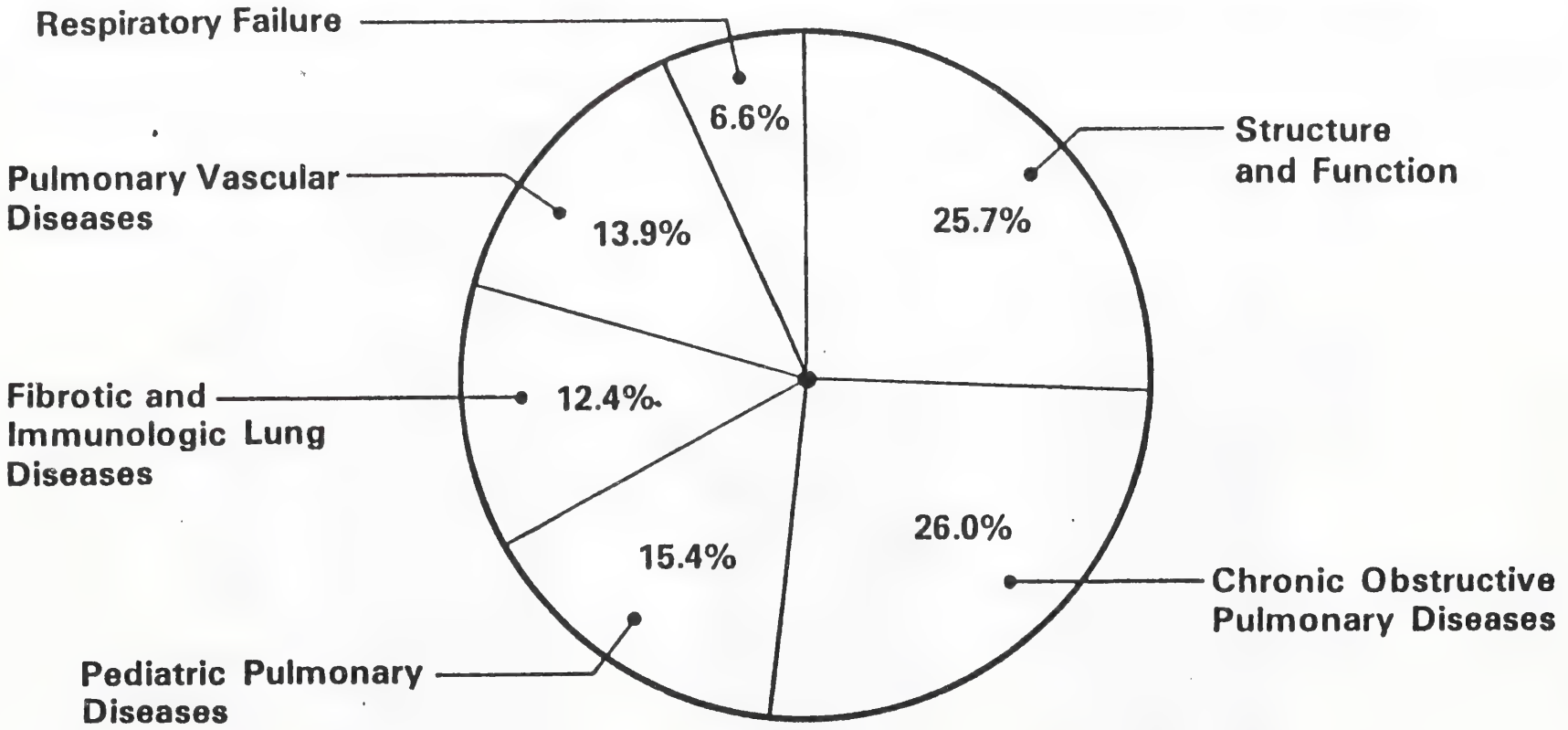
Division of Lung Diseases
Budget History



Slide 3

Division of Lung Diseases

NATIONAL PLAN CATEGORIES



FY 1981 Total: $78.908M

Chronic Obstructive Pulmonary Disease: $20.516M

About one-fourth of the Division's budget is devoted to the basic studies of lung structure and function. A slightly larger amount is allocated to studies of chronic obstructive lung diseases.

Chronic bronchitis and emphysema, the diseases receiving major emphasis in the program area, are progressive, debilitating disorders that are irreversible by the time they are diagnosed and for which, at present, treatment is only palliative. Hence, the primary research focus is on prevention of these diseases through an understanding of risk factors and on measures to arrest their progression.

Asthma, the other chronic obstructive lung disease covered in this program, is being studied mainly with regard to mechanisms involved in broncho-constriction and development of therapeutic intervention. Cystic fibrosis and bronchiolitis, which are also obstructive lung diseases, are covered in our program on pediatric pulmonary diseases.

Rather than proceed with an inventory of the other significant activities of the Division of Lung Diseases, however, I wish to emphasize a non-categorical program whose success is crucial to all the rest for the present and into the future.

As I indicated earlier, a major obstacle to advances in pulmonary research was the gap that existed between investigators in the basic sciences and practitioners aware of the clinical realities of pulmonary disease.

When the Division was established, one of its first actions was to set in motion programs for development of manpower. Special pulmonary training programs were developed within the framework of the existing NIH training mechanisms--the National Research Service Awards and the Research Career Development Awards.

The Division initiated Pulmonary Academic Awards and Pulmonary Faculty Training Grants to designated training centers, and awards for "junior faculty" from other institutions who receive training at the designated centers.

The objective of these programs is to attract competent physicians and scientists to the practice of pulmonary medicine and to provide training for physicians and scientists for research and academic careers.

Sixty-five medical schools have received Pulmonary Academic Awards since the inception of the program.

(SLIDE 4) Pulmonary Academic Award

While it is the general impression of all who have been involved in this Pulmonary Academic Award Program that it has been a very successful program, the Division is obtaining a more objective assessment through a contract to evaluate the impact of the program.

A more general and rather spectacular assessment of the success of the efforts to bring together the concerned clinical and research scientists in the field of pulmonary research can be seen in the mix of Ph.D.s and M.D.s in the various training programs supported by the Division.

(SLIDE 5) "Individual Support for Postdoctoral Trainees"

M.D.- Ph.D. Distribution, 1980

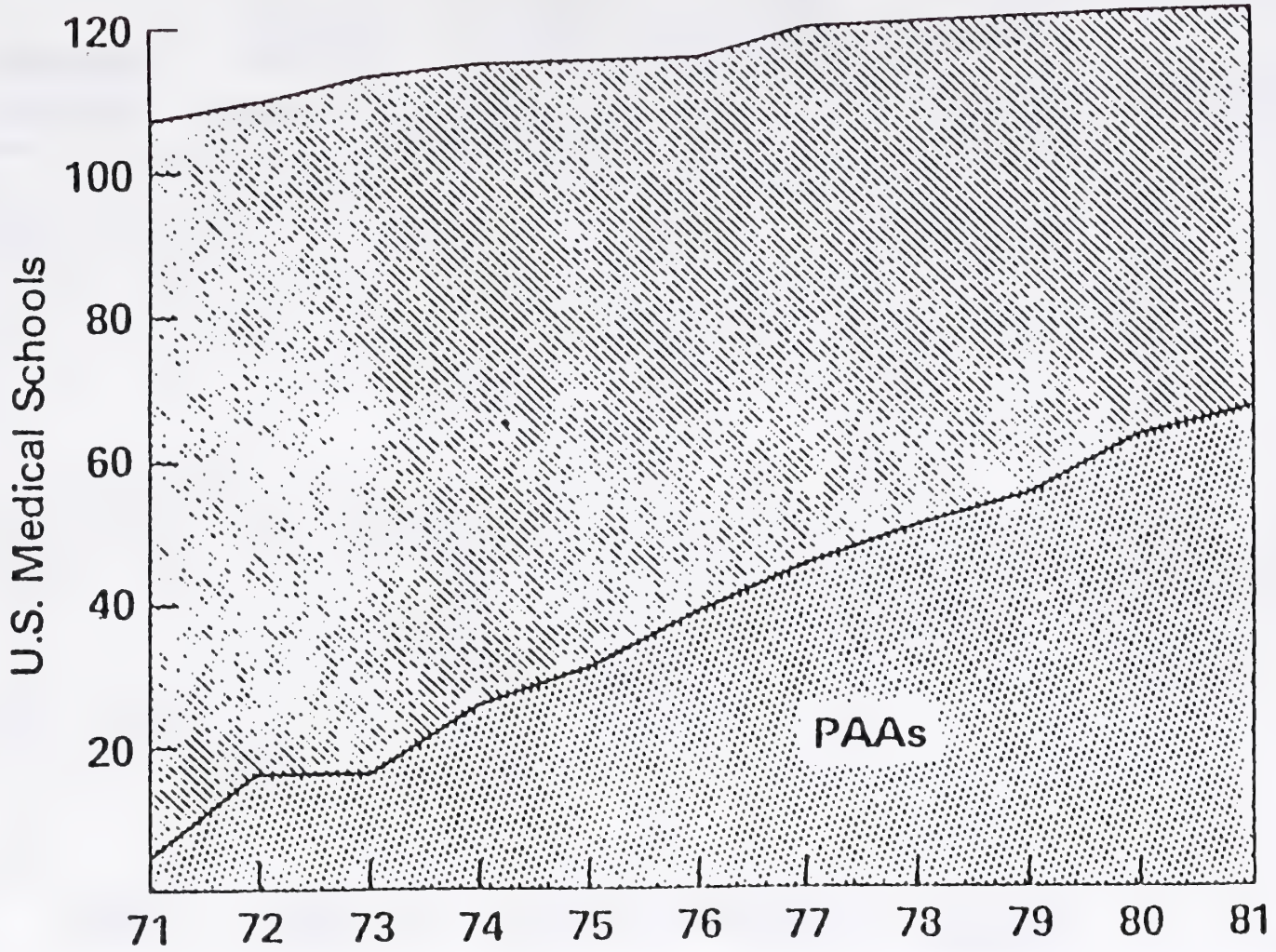
(SLIDE 6) "Support by NRSA Institutional Grants

M.D.-Ph.D.

When compared with the total of NRSA training programs sponsored by the NIH, the Division of Lung Diseases programs show a very high percentage of M.D.

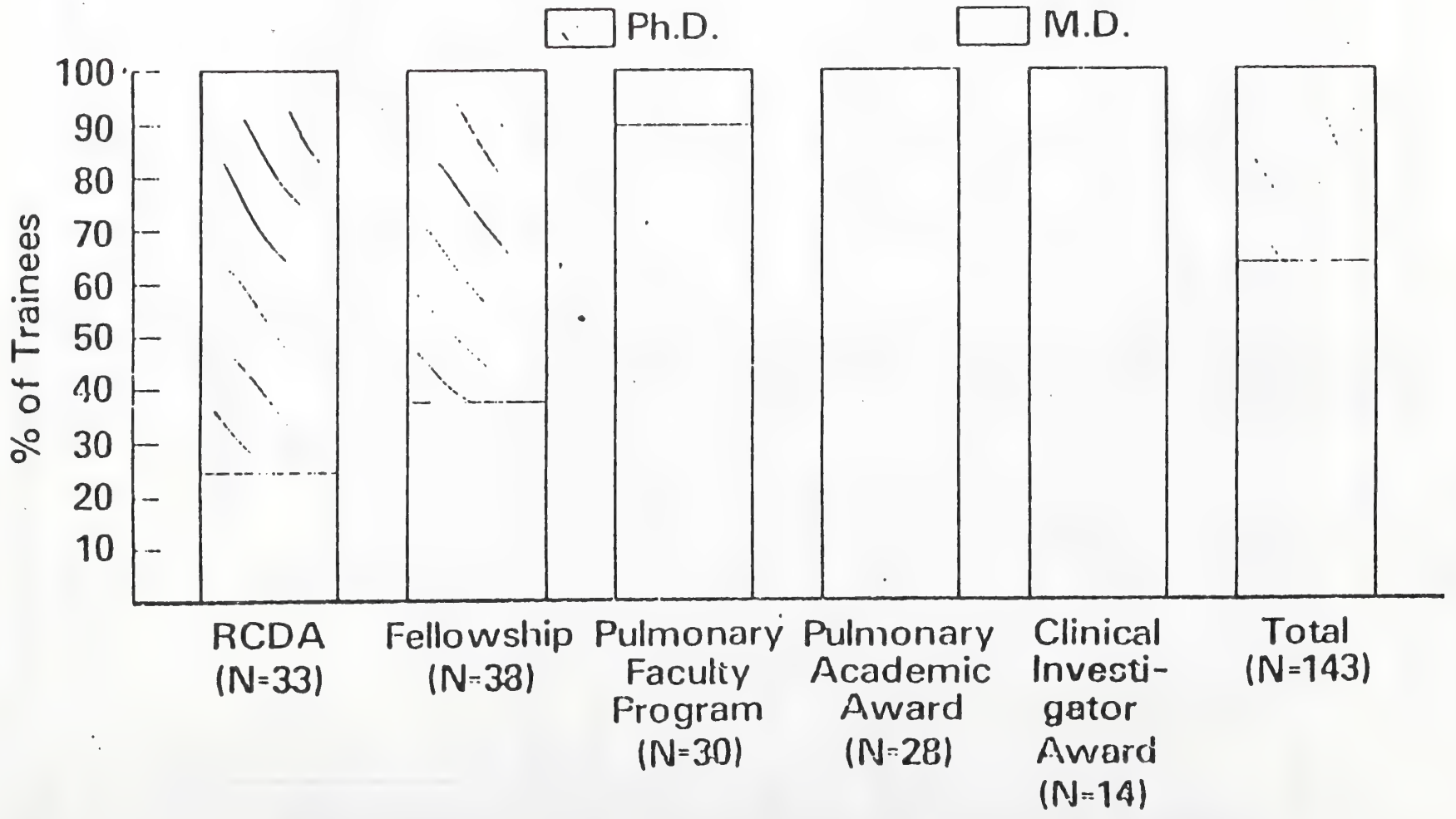
Slide 4

Pulmonary Academic Award Growth of Program, 1971-1981



Division of Lung Diseases

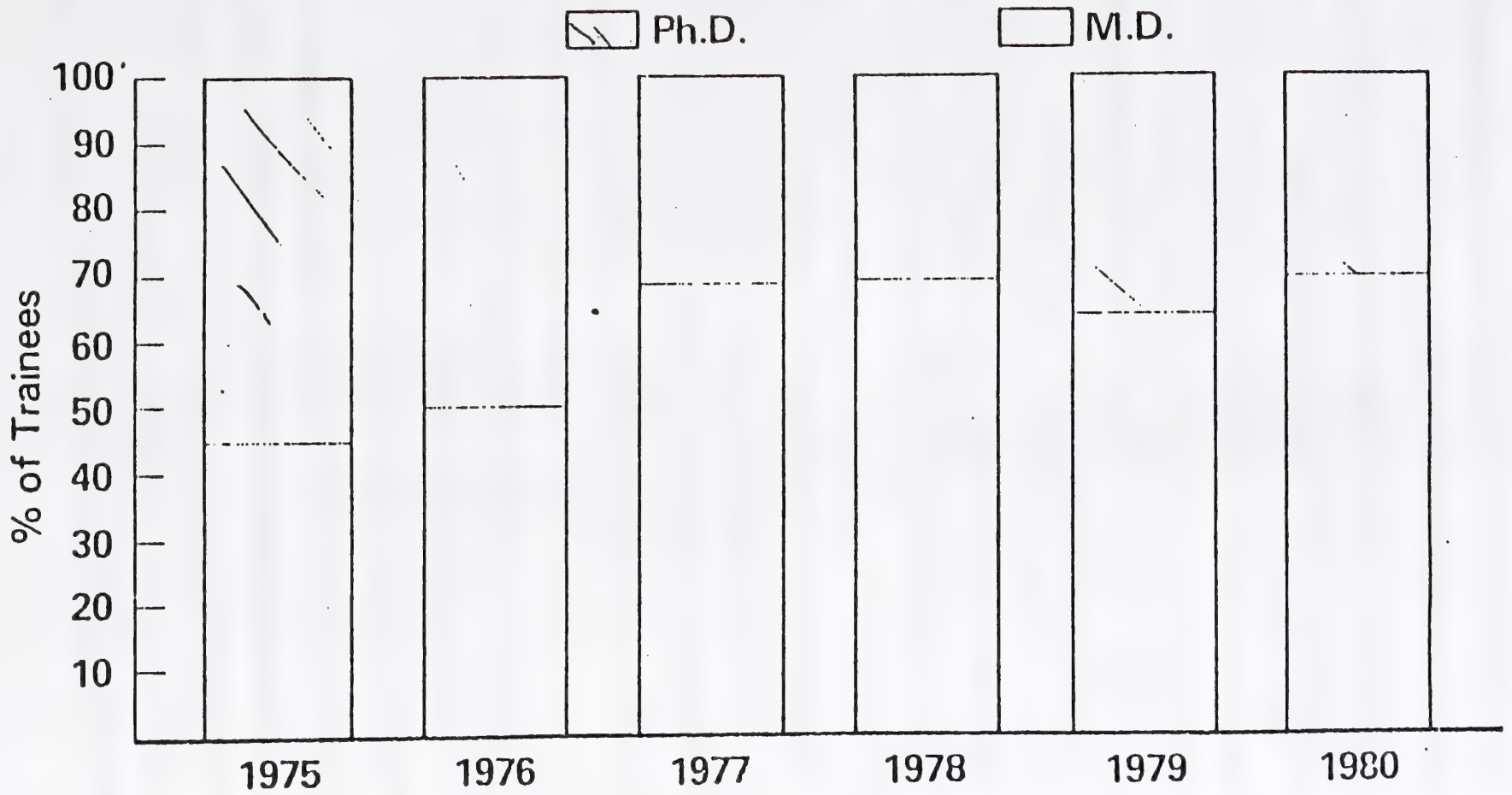
Individual Support for Postdoctoral Trainees
M.D.-Ph.D. Distribution, 1980



Slide 6

Division of Lung Diseases

Support by NRSA Institutional Grants
M.D.-Ph.D. Distribution



participation—about 65 percent. This is almost three times the percentage of physician participation in all NIH postdoctoral training programs.

Certainly the success of this effort of the Division will have a lasting effect on the range and quality of research against pulmonary disease.

I mentioned earlier that I have just begun my freshman year as Director of the National Institutes of Health. In fact, this is my first significant public appearance in the role of Director. Perhaps I should say a few words about myself and about my general views on biomedical research and the issues facing NIH.

I have had an association with NIH in various positions through the years. It could scarcely have been otherwise since NIH plays a unique and wide-ranging role in the field of biomedical research.

Before beginning my academic teaching and administrative career, I conducted research at the National Heart Institute, and at what was called the National Institute of Arthritis and Metabolic Diseases. Over the years I have also served as a member of a number of advisory committees to components of the NIH.

I am well aware that this is a critical period for NIH and the field of biomedical research. The explosion of biomedical knowledge and improved technology in recent years offers greater opportunity for advances in medicine and health than ever before. At the same time, we must face the reality of economic constraints.

I am strongly committed to the pursuit of basic research as the foundation for the understanding, treatment, and prevention of disease and disability. Equally, I believe the investigator-initiated research holds the greatest promise for significant discoveries. History clearly shows that the great advances come through hard work by dedicated individuals and teams pursuing their own creative ideas.

One of my major goals as Director will be to preserve the traditional emphasis of NIH on basic research and training as the bedrocks upon which all the rest of its program structure is built. As a corollary to emphasis on investigator-initiated research, I am also committed to support for research training, for both physician and Ph.D. research scientists. Clearly, if we are to have excellence and continuity in research, we must train scientists to carry on this work in the future.

I believe we must make every effort to maintain the momentum of scientific research and discovery achieved in recent decades, achievements based on many years of work in basic science. The intramural research program and the Clinical Center at NIH are key elements in the search for biomedical knowledge that extends across the nation and throughout the world. Our recent advances in scientific understanding are being translated into medical practice and the result is improving health and well-being for all.

The kind of research necessary for such advances is highly complex, demanding well-trained investigators and sophisticated instruments. Not surprisingly, this work is expensive. And that fact, coupled with a need for budgetary restraint, places a high premium on sound decisions. Difficult choices are unavoidable and we must be prepared to make them.

We must set priorities wisely, emphasizing our investigator-initiated research and relying on the system of study sections and advisory councils by which we weigh proposals and monitor progress in research. We must continue to manage our programs for maximum efficiency and effectiveness as we invest in areas of high promise in pursuit of the NIH mission to understand, treat, and prevent disease and disability.

In addition to maximum effort on the part of the dedicated staff and the responsible officials of the NIH, our success will depend upon the continued understanding and support of organizations like the American Lung Association.

For the latter reason, I was especially pleased to be invited to join you on this occasion--to tell you of our aspirations and concerns, to renew old acquaintances among your leaders, and to meet many others with whom we will be working in the challenging years ahead.

Transcript of

Dr. James B. Wyngaarden's presentation

at the

Rockefeller Archive Center

Conference on
Academic Medicine, Present and Future

Tarrytown, New York
May 26, 1982

(The following is the separately transcribed presentation from the Wednesday afternoon session, May 26, 1982.)

DR. JAMES B. WYNGAARDEN: I appreciate this opportunity to speak to you about careers in academic medicine. When I accepted the invitation last summer, before word of the NIH appointment had come along, I was to be addressing you as chairman of a department of medicine, and I will speak chiefly from that vantage point today. I should begin, though, by pointing out that in my new role I have a somewhat wider perspective.

The development of careers in academic medicine has long been a major function of departments of medicine, particularly those that have a strong research emphasis. The opportunities in such departments have depended heavily for the past two or three decades on the relationship between the Federal Government and the medical schools. Ideally, I suppose, the topic should be approached in a general fashion--academic medicine with a small "m." But my experience doesn't really extend to very many fields. What I say will apply chiefly to departments of medicine.

Most of us in this room are products of a medical school based on the Flexnerian model.

We are dedicated to the bioscientific strategy of medicine, and that indeed has oriented most medical schools since World War I. Another powerful impetus toward that strategy has been the impact of NIH on the structure of medical schools. All of us date from pre-World War II, and most of us go back to the days before the NIH influence. We have all lived through the period of tremendous change that brought us where we are today.

In many ways the most significant phase is what I like to refer to as the Shannon era, which started at NIH about 1955 and ended about 1968.

I read recently some reflections by Dr. Sebrell, Director of NIH just before Shannon. Sebrell pointed out that when he became Director in 1950, the budget was $52 million, and when he left NIH five years later, it was about $80 million. That, then, was the budget when Dr. Shannon took over. When Shannon left 13 years later, the NIH budget was around $1 billion and still growing rapidly.* During those years some incredible challenges were met with steady brilliance and good judgment, to benefit not only NIH

*A strict comparison should take into account that the 1968 NIH appropriation of $1,179 million no longer included the National Institute of Mental Health, which had become a separate bureau of the Public Health Service in 1967.

but medical schools and American medical education as well.

With the increase in funds that came to NIH at that time, there was an opportunity to devise a strategy for the conduct of research that extended far beyond NIH itself. When Dr. Shannon became Director, there was a grant mechanism in place, to be sure, but the intramural program budget was a very much larger fraction of the total than it is today. The bulk of new money went into biomedical research conducted outside NIH through its extramural program. The grant mechanism evolved to strengthen the new modalities that were developed, such as program project grants, center grants (on a relatively small scale then), and training, which averaged about 18 percent of annual obligations throughout the Shannon era.

The training grant and the direct fellowship were sharpened and expanded. Like the research grants, they operated under a peer review system, which was adapted to cover all types of awards as they were instituted.

All of this profoundly influenced the structure and function of the medical schools, and perhaps affected the department of medicine as much as any department.

Prior to the influence of NIH, research on medical problems was largely a part-time activity. By the end of the Shannon era, it had become a professional life for many people. And it exerted a kind of influence in the department of medicine that Gene Kennedy and Al Lehninger commented on earlier, where basic and clinical scientists were able to collaborate to their mutual benefit.

All of that sailed along nicely, creating a dependency that no one worried about then--at least, not enough to turn down NIH dollars. The dependency has had various effects. It has diverted the orientation and loyalties of faculty, for example. Many faculty members now feel more dependent on NIH for funding support than they do on their own department chairman or dean.

From the institutional point of view, there arose an intense dependency of another kind. This has been brought home to me--particularly in the last few months--as I talk with more and more university administrators on proposed cuts in indirect costs, which is a devastating prospect to many institutions.

I think back to the 1960's, when in the course of the Vietnam conflict, many of the established values were challenged--challenged by medical students whose interests changed remarkably.

Prior to that time the typical applicant for a medical internship would express the intention of going into biomedical research at NIH and then into academic medicine. However, not nearly so many did that as said they would. They often gave that answer, I'm sure, because they thought that's what we wanted to hear. Nevertheless, research did represent the major interest of a large number of medical students. Then their attitude changed dramatically during the Vietnam conflict, as studies have shown.

A challenge to the whole Flexnerian strategy of medical education erupted. The critics proposed that the bioscientific strategy of medicine had been erroneous from the start, and that the great advances in health care had really resulted from improved sanitation and improved nutrition. To support their claim, they showed that death rates from tuberculosis and other infectious diseases had dropped substantially before the advent of antibiotics. They suggested that the money spent on biomedical research was unjustified and that the results were far too meager to warrant a continuation of that strategy.

All those points, I think, can be effectively answered. But they were voiced,

nonetheless, and an alternative strategy--an "ecological strategy for health"--was advanced. In my view this is not really an alternative to the bioscientific strategy, but rather a coordinate, perhaps independently justifiable strategy.

I think some of the changes in life style mentioned earlier today--reduced smoking, proper diet and proper exercise, behavioral changes of that sort--have played a role that is quantitatively uncertain in relation to the death rate from cardiovascular disease, but may have contributed to the decline from 522 (per 100,000 population) to 450 between 1968 and 1978.* Health progress is usually due to a mixture of influences. Control of hypertension, for example--a development based on the bioscientific strategy--certainly ranks with any advance achieved through alternative approaches. Both strategies are probably valid. We have seen support for both around the table today.

The dependency on NIH mechanisms is a topic I would like to spend a little more time on, and also the change in attitude that developed among students and the house staff. I am referring to the profound influence of changes in the philosophy of government support for training that took place

*Includes four categories of diseases of the circulatory system--diseases of the heart, cerebrovascular disease, arteriosclerosis, and hypertension.

during the Nixon administration.

You will be interested in some of the quantitative aspects of the utilization of NIH training devices by medical students and fellows over the past decade. We might start with Figure 1, which tabulates the total number of NIH trainees and fellows from 1969 to 1983 (est.) in terms of full-time equivalents. You can see a gradual decline to an estimated low of about one-half the 1969 level.

Figure 2 shifts to actual numbers for the years 1971-81. You can see that back in 1971 about 60 percent of all postdoctoral traineeships were held by M.D.'s (or M.D.-Ph.D.'s) and that this vehicle was used to a much lesser extent for the training of Ph.D.'s. The subsequent years saw a shift in these ratios, with a crossover around 1975. Specifically, the number of Ph.D.'s utilizing the institutional and individual awards increased, while the number of M.D.'s decreased from 4,634 in 1971 to 1,961 in 1980.

In terms of funding, the turning point was in 1973, when the Nixon administration impounded funds and blocked new awards for fellowships and traineeships. Training awards came back the following year, but with remarkably different criteria and new legislative authority--the National Research Service Award Act.

The traineeships in the 1950's, as they emerged during the growth of NIH, had a variety of purposes. These included production of skilled clinicians in areas where medical expertise was considered to be poorly represented. Diabetes training grants, for instance, were designed to train diabetes specialists to work in communities. Many of the people in the professional traineeship category were individuals who had predominantly clinical interests.

Under the NRSA Act of 1974, the National Academy of Sciences was asked to speak to the need for training and to advise Congress annually on the training areas and the numbers of trainees needed in each. I was privileged to serve on that committee. We clearly did not know how many of the 4,200 individuals in clinical training positions--3,200 trainees and 1,000 fellows--had academic interests at heart, but we estimated that perhaps two-thirds did and therefore recommended that 2,800 such positions be awarded annually.

Well, as you can see, the number of M.D.'s utilizing NIH traineeships dropped sharply. It leveled off around 1976. That probably represents to a large extent the disappearance of the purely clinical trainee. But also the award came with a pay-back requirement that may have acted as a disincentive for some.

Figure 3 focuses on postdoctoral trainees and fellows. You can see the dramatic drop in M.D.'s as a percent of total postdoctorals. Meanwhile, however, there is an increase in total postdoctorals as a percent of total awardees. The downward trend in M.D. applicants probably reflects several factors, including the economic disadvantages of a biomedical science career. It may be noted that the trend is concurrent with increases in medical school enrollment and the production of physicians.

Turning to the research grant programs, some figures on the M.D. as principal investigator (P.I.) have received quite a lot of publicity and have reached the Congress through public testimony. Members of Congress view the data as an alarming trend in biomedical science. They are concerned about the decline in the number of M.D.'s receiving traditional investigator-initiated research grants (ROIs). These dropped from 4,000 in 1966 to 2,943 in 1980. M.D.'s as <u>new</u> P.I.'s are leading the trend, dropping from 487 in 1966 to 252 in 1980.

In relative terms, the M.D.'s in 1966 were about 40 percent of all P.I.'s on R01 grants and dropped to 23 percent in 1980. As new P.I.'s, M.D.'s dropped from about 40 to 20 percent over the same period.

It should be pointed out that the number of R01 grants awarded to holders of professional degrees has really increased--from about 10,000 in 1966 to 12,600 in 1980. Thus the trend is upward for the Ph.D.'s, who have just about doubled over the same period. Likewise, those with combined degrees--M.D.'s with a Ph.D. or equivalent doctorate--have increased from about 650 in 1966 to 1,100 in 1980.

The decline in the number and proportion of M.D.'s on R01 grants reflects two trends. The most significant is a relative drop in applications. Looking at all competing R01s, we see that M.D.'s comprised about 30 percent (1,843) of the applicants in 1970 and only 24 percent (2,775) in 1980. The second trend is the declining success of M.D.'s in obtaining grants, notably in the past six years. Among new M.D. applicants on new R01 projects, 50 percent (of 615 applicants) obtained awards in 1974, whereas only 30 percent (of 795) succeeded in 1980. By contrast, the Ph.D. success rate in the latter year was 38 percent. M.D.'s have averaged about 6 percent below Ph.D.'s in grant-winning success since 1975. The principal reason for failure of M.D. applications seems to be deficiencies in experimental design.

I will also mention that the New Investigator Research Award, introduced in 1971 (as the Young Investigator Award), continues to attract

M.D.'s and Ph.D.'s about equally. These awards support junior faculty in specific disciplines. The program has grown steadily after a modest start.

But in the overall, it is clear that the M.D. as a research trainee or an independent investigator (in contrast to a P.I. on the larger grants--program projects and centers) has not kept pace with the growth of the system in general.

The disincentives that have grown up affect the choice of young physicians in the province of medicine and careers. I think the perturbations of the Vietnam era have probably come and gone to a large extent, but we are now left with an economic situation that is drastically changed.

The debt load of medical students has grown enormously. I don't know the average now, but it is frequently $30,000 or $40,000 upon graduation. Training stipends have not kept pace, though they have been increased from time to time. They average 26 percent less than the residency stipend.

Clinical training has been gradually lengthened. In the research-intensive medical schools in particular, where most interns finish their general medicine and enter a specialty program, the usual minimum of training is now five years.

All of that is to be contrasted with the rather extraordinary sums to be earned in practice,

particularly in procedure-based subspecialties of medicine. We are seeing the rise of what one of my former chief residents called the resident-fellow-Porsche syndrome. Economic factors were always a counter-attraction to the academic life, but I believe this was much less the case when most of us made the decision to join.

In the field of internal medicine the American Board of Internal Medicine, in my judgment, has had a somewhat inhibitory influence through the rigidity of its clinical training requirements for certification. Recently they have been modified substantially.

There was a time when short-tracking was permitted. One was allowed to take two years of general medicine, then start a subspecialty training program and apply the first year of that program toward both the general medicine and the subspecialty board requirements. In that manner one could finish in four years, five in some fields, rather than five or six.

Initially, only a small fraction of the residents in medicine, 10 or 15 percent, took the short track. But the trend increased. It was perceived that the short track was encouraging residents to choose a subspecialty career just at the time that general medicine was thought to need expansion, and

so the short track was discontinued. That decision forced residents into a standard pattern that didn't allow much flexibility for research.

A third and very important influence--which David covered nicely and I think Al Lehninger touched upon--is that so many students have no basis on which to choose a research career because of a lack of laboratory experience in the medical school. I've talked with many residents whose laboratory experience consisted exclusively of anatomical dissection demonstrations. The jettisoning of lab experience in biochemistry or microbiology or pharmacology has been a major loss.

The Duke curriculum is an exception. It offers an alternative for acquiring laboratory experience in the third year.

And the disappearance of the NIH post-sophomore fellowship didn't help. About a year ago NIH put back into the system a three-month research opportunity for medical students. This is available to any given student, sometimes for three consecutive years. About a thousand medical students with such support got into the laboratory for a summer or an off-quarter. I'd like to see that time extended. But not every student has a good experience the first three months, and if it turns out poorly, the experience may actually have a negative impact.

The pay-back provision of the NRSA has been a disincentive, more for the M.D.'s than the Ph.D.'s. A Ph.D. who accepts a training award has already made a career decision, but the M.D., about to take the first step into the research world and as yet uncommitted, may be deterred by the pay-back requirement. The Reconciliation Act of August 13, 1981, modified the payback obligation, and pending legislation would abolish it altogether.

Another factor acting as a disincentive for the M.D. trainee is the growing sophistication of science and the professionalization of science in clinical departments. The finest medical education and the finest resident training in the world do not equip the young physician to function effectively in the laboratory.

There is a large gap between the bedside and the bench, and one needs to spend a substantial amount of time acquiring new skills to be successful in research. Fellows realize that with the intense competition for grants, one has to decide whether to invest heavily in research training or not at all. This isn't conducive to getting them just to try it. Nevertheless, there are splendid opportunities for those who make the necessary investment. In my opinion two years of full-time research training is a marginal minimum; three or

four years are much better.

Now we might look briefly at the problems of size of departments and size of schools. The AAMC figures indicate that clinical departments have about 1,000 new faculty positions available each year and about 2,000 additional positions from attrition and turnover. These may sound like large numbers, but given 125 medical schools, it's really about 8 new appointments annually per school and maybe 16 turnover positions, or a total of 24. That's only two or three per clinical department.

One of the interesting facts that came out of a recent AAMC study is that only 21 percent of those who received new appointments to clinical departments from 1975 to 1978 had had any postdoctoral research training. This is not difficult to understand when you realize that many of these are clinical appointments. In departments of medicine, for example, clinicians in the outpatient department, or those who run the cardiac catheterization lab, may have had no research training.

But it is also rather alarming, from the standpoint of the tone set for the training of medical students, that more than three-quarters of the young faculty have never conducted research or had any research training.

On the research front, the prospects of support are still good, though not as generous as they used to be. Personally, I think the Hoechst and Monsanto types of award are anomalies and won't be widely replicated. I don't view such developments as a general solution for the support of medical science. Industrial competition may provide some new alternatives. There have been about 150 new biotechnology firms formed in the last couple of years, but I suspect that half of those will disappear shortly.

Of course, there is still a substantial Federal budget. We are in a period of painful readjustment, but $3.6 billion still enables us to support a lot of very good science.

The competition will be greater, and we can expect the best trained people to be the most successful. It is clear from our analyses that training at NIH or in NIH postdoctoral fellowships or traineeships greatly extends the lifetime of the research grantee.

For those who have been in the system since 1965, such experience has increased the median survival time by a factor of 2. The median figure for Ph.D.'s who had trained with NIH support was something like 11 years under NIH grants. Clearly, those who have obtained training and retraining stay in the system a good deal longer.

One of the stresses on the system, which is not always apparent from the numbers, is the extent to which physician investigators are being replaced by Ph.D.'s. Even in departments of medicine, this tendency is growing. I am not saying that the trend is necessarily undesirable, but it is clearly discernible.

Of the 2,800 traineeships earmarked for clinical departments each year, about 1,900 are filled by M.D.'s and 900 by Ph.D.'s. The Ph.D. fraction has been steadily mounting. It's 30 percent this year--up from 20 percent only three years ago.

One of the complex issues today is the Federal policy of stabilization. As a department chairman in a university, I thought it was splendid, because the policy of giving the highest priority to roughly 5,000 new grant starts per year (but slated to be less this year) represents one of the most solid encouragements to the young investigator.

The stabilization policy has had some major consequences. Placing the highest priority on the investigator-initiated award has resulted in certain readjustments. For example, there has been a decrease in the number and dollar amounts of research contracts and centers. The Institute Directors are concerned about this because it has limited the

flexibility of management.

Obviously the system has become very tight. There is strong competition among the various kinds of support.

A magnificant partnership has evolved between universities and government, and I certainly would like to do everything I can to preserve that. We are collectively seeking ways to minimize the strains.

One of the problems is to preserve the interest of a reasonable number of physicians in a scientifically oriented career. Fortunately, the supply of Ph.D.'s in the biomedical sciences has held up well. But I think the balance between Ph.D. and M.D. scientists that has existed until just recently would be a good one to maintain. We need to encourage young physicians to enter the world of science-in-medicine. Indeed, there are magnificent opportunities. One thinks of the implications of recombinant DNA, the explosion in the neural sciences, and other advances that should make the next decade unusually bright.

DR. BOWERS: Thank you, Jim. Please don't forget that a significant degree of Jim Shannon's success was the fact that he had a Senator and a Congressman giving him close support, namely

Senator Lister Hill of Alabama and a man named Fogarty from Rhode Island.

(The afternoon session adjourned 5:30 p.m.)

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Figure 1

NUMBERS OF TRAINEES AND FELLOWS
ON NIH RESEARCH TRAINING AWARDS
1969-1983 Est.

(Full-Time Equivalents)

Year	Number
1969	16,138
1970	14,810
1971	14,288
1972	14,613
1973	12,675
1974	13,547
1975	12,272
1976	9,654
1977	10,198
1978	11,123
1979	11,197
1980	10,664
1981	10,695
1982 Est.	9,702
1983 Est.	8,915

Figure 2

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81

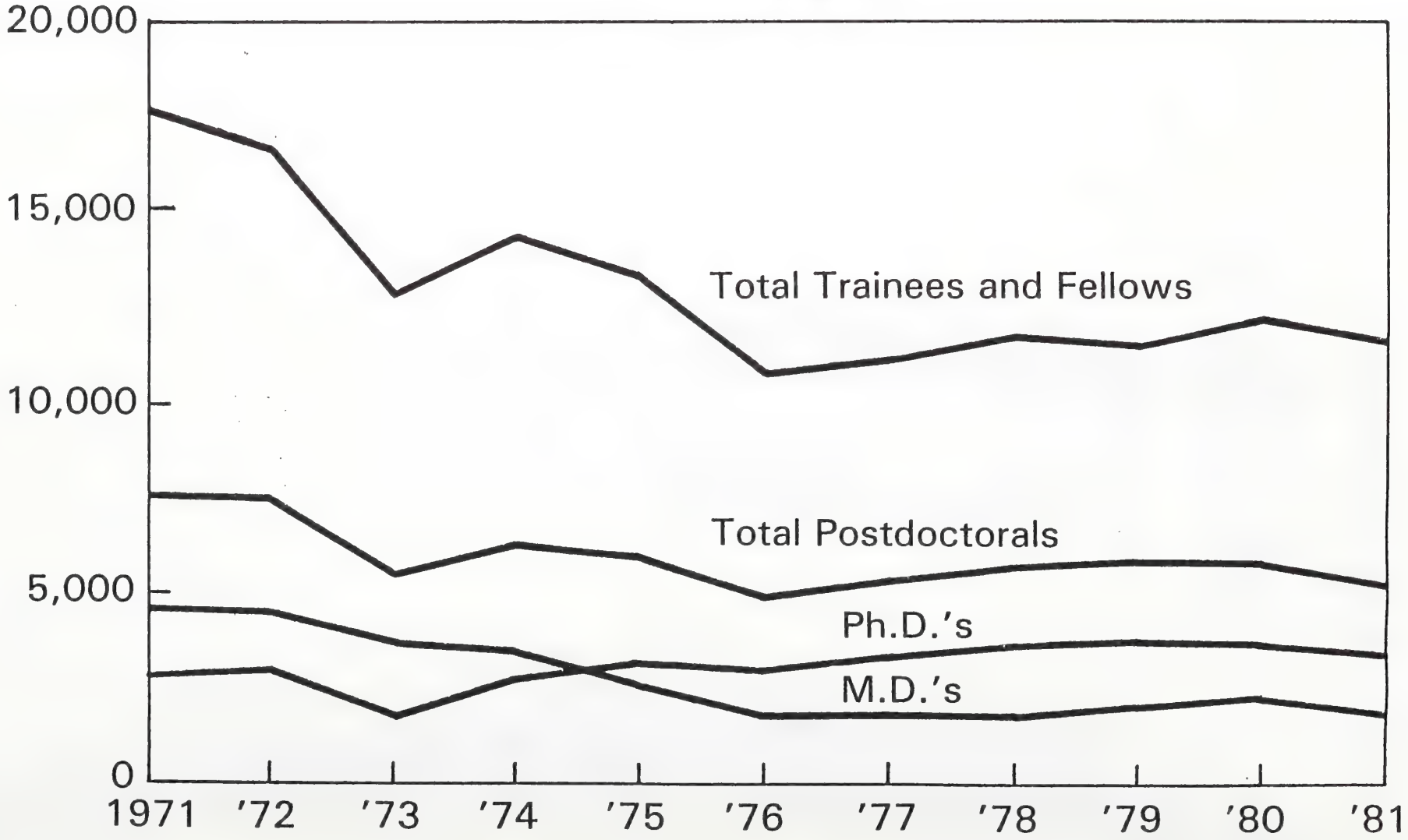
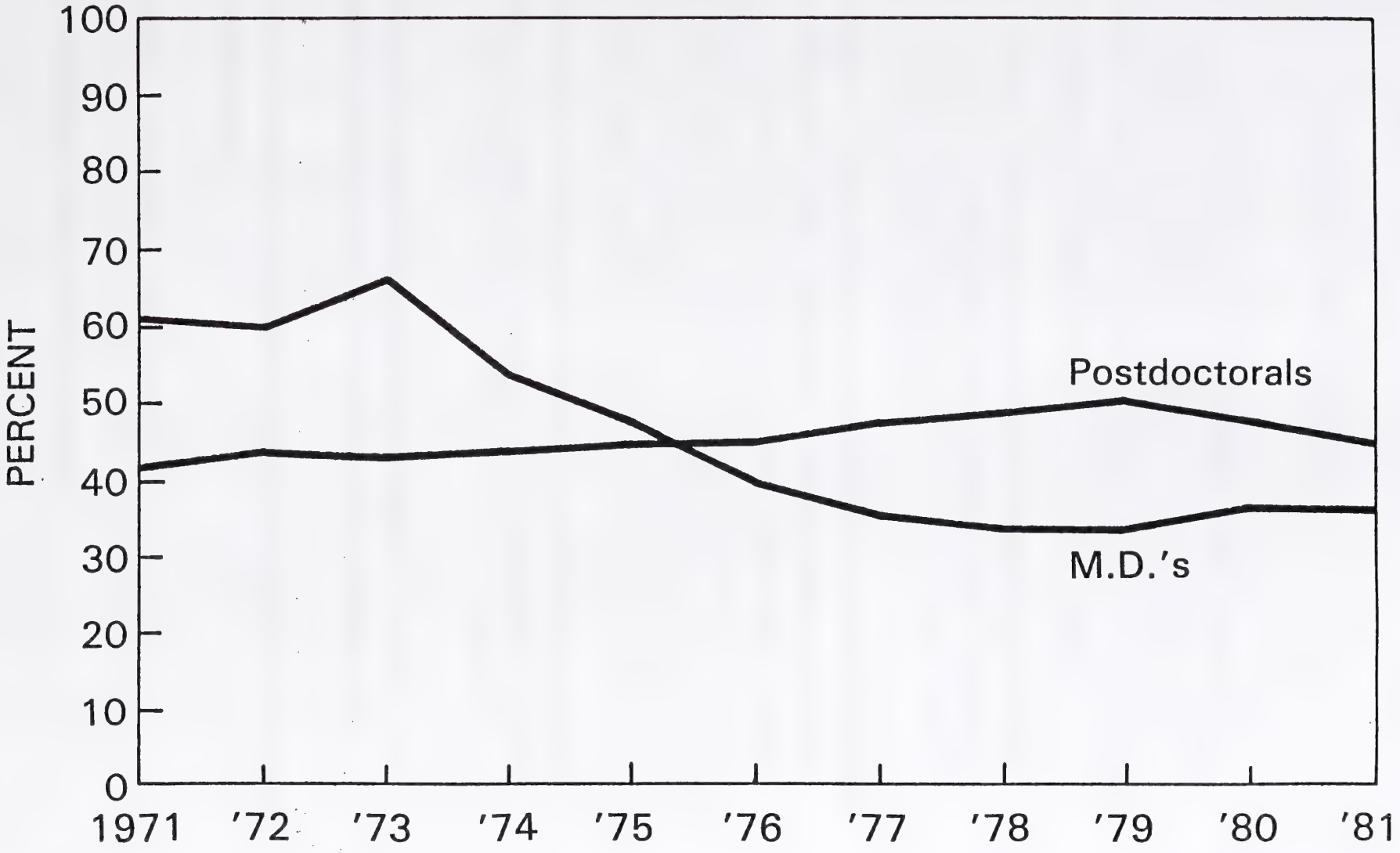


Figure 3

POSTDOCTORALS AS PERCENT OF TOTAL NIH TRAINEES AND FELLOWS, AND M.D.'S AS PERCENT OF TOTAL POSTDOCTORALS 1971-81



REMARKS*

by

James B. Wyngaarden, M.D.**

Dr. Pickett, because of your able and active assistance, I view my role as NIH Chairman of the 1982 Savings Bond Campaign with optimism and confidence. You have described very well the features of the Savings Bonds that make them an attractive investment opportunity for all members of the NIH community. They offer a flexible and simple means for everyone to set up or improve upon a regular savings program.

I am grateful to you Dr. Pickett, and your associates, for organizing this campaign. And to all the workers who will be participating in the campaign, I want to express my appreciation in advance for the time and effort you will devote to the task of reminding your fellow employees of the benefits of Savings Bonds.

The decision to invest in Savings Bonds or to increase present purchases must be left up to the individual employee, of course. It is our task, however, to make sure that such decisions are made on the basis of full and current information. The materials you have, the presentations at today's rally, and the briefings you have been given will serve to inform you so that you can inform others. As a matter of institutional pride, we naturally are interested in having a good level of participation by all segments of the NIH — and that depends in large part on how well we spread the word. That is our challenge.

I welcome the opportunity to participate in this kickoff rally and serve as Chairman of this year's Savings Bond Campaign because it gives me my first opportunity to speak to a general meeting of NIH personnel — not about problems — but about an opportunity shared by all of us.

In returning after having been a part of this institution nearly 30 years ago, I am impressed once again by the people of NIH. Truly, we are part of an unusually fine community.

I wish you well in the service you will render by acquainting your co-workers with the advantages in U.S. Savings Bonds.

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*Presented at the 1982 U.S. Savings Bond Kickoff Rally, Masur Auditorium on June 3, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

Welcome to the National Institutes of Health and to the Annual Honors Convocation of the Career Education Institute.

I am pleased to join in honoring the graduates of this program which offers advanced education to all who want to learn, through cooperation of the Department of Health and Human Services and the University of the District of Columbia.

It is appropriate that we asssemble here at NIH on this occasion to pay tribute to achevement in learning. After all, the basic mission of NIH is the pursuit of knowledge. Through the years, this hall, and this campus, have been host to some of the world's greatest scientists and scholars. No matter what level or area of learning, all share one common goal--the advancement of knowledge and understanding. The graduates here today, through their efforts, have earned a place in the community of seekers of knowledge.

They have discovered, I am sure, that learning is never complete. It is a continuing process; one corner of knowledge turned reveals yet another avenue of learning to pursue. Learning is among the most satisfying and lasting of human endeavors and pleasures.

(I should warn you also that learning is addictive -- once tasted, it is difficult to resist more. And, it is one of the few pleasures in life that is neither fattening nor sinful.)

The benefits of the Career Education Institute extend beyond the enrichment of the lives of individual participants. The NIH and many other agencies of the Department for which they work are beneficiaries, too. Education is many areas enables the students and graduates to perform their duties more effectively, to broaden areas of competence, to assume greater responsibility as their careers advance, and to enjoy their work more. Everyone benefits.

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*Presented at the Eighth Annual Career Education Honors Convocation, Bethesda, Maryland, on June 4, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

Since its founding 11 years ago, the Department's Career Education Institute has graduated 311 baccalaureate candidates, 116 Associate Degree candidates, and two Master's Degree candidates. The program has recognized 613 honor students and 14 employees have been inducted into "Who's Who in American Colleges and Universities."

The diplomas, certificates, and honors presented today mark education achievements. But they do more -- they are a tribute to your determination, dedication, and plain perseverance. It is not easy to perform a full-time job and fulfill family responsibilities while pursuing a course of advanced study.

Many of you have devoted years to the achievement of the academic goals we recognize today. I am certain that, over the years, many lawns remained uncut, many meals were delayed, and many pleasures were foregone during the course of study.

So, we pay tribute today to the students and graduates on their achievement. We also recognize the supervisors and fellow workers who offered encouragement, and the families who provided support and understanding.

To the graduates and honorees, I offer a reminder that today marks an end and a beginning -- the end of one educational effort and the beginning of another.

My congratulations on your achievement and best wishes for the future.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

It is a personal privilege for me as a member of the scientific community as well as a representative of the Government of your host country to extend a warm welcome to each of you. Since the opportunities for the United States to serve as host for this Pan-American Conference are spaced almost a quarter century apart, I feel especially fortunate to have come on the Washington scene just in time to be chosen to greet so many friends and colleagues whose professional interests and endeavors so closely parallel my own.

Such fortuitous timing also makes it possible for me to share the platform for a moment with your presiding officer, my longtime friend--Larry Shulman--and to tell this audience of the respect and admiration in which he is held by his NIH colleagues. How pleased we are at the honor the League has accorded him!

As one who has followed developments in the field of rheumatology with more than average enthusiasm, I have found the program you have ahead of you to be a rich and exciting one. In a tangible way, it is an index of the increasing breadth and depth of understanding of the challenging diseases with which you are concerned, and I am aware that much of that progress can be credited to the men and women who make up the membership of this Congress. The content of your program illustrates the spectacular discoveries in the life sciences in recent years.

In looking at the subjects that will be presented in your Scientific Sessions during the coming week, I noted a number of topics that could not possibly have been discussed in 1959, the last time the Pan-American Congress of Rheumatology met in the United States. The reason is obvious--current research is using powerful tools like monoclonal antibodies and recombinant DNA, which simply were unknown 20 years ago. These techniques represent tremendous increments in knowledge. As is so often the case, these techniques emerged from studies in the basic mechanisms of biology--studies whose only immediate goal was better understanding. There was little precognition as to ways in

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*Presented before the VIII Pan-American Congress of Rheumatology, Washington, D.C., on June 7, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

which this new knowledge could be applied. This illustrates the underlying unity of basic research, and reminds us that we must not falter in our dedication to the quest for basic knowledge.

That is why the highest priority on my agenda in assuming the position of Director of the National Institutes of Health is to continue to emphasize the support of basic biomedical science with preference given to the investigator-initiated grant mechanism. At present, about 50 percent of the NIH budget is expended in the support of research projects proposed by individual nonfederal scientists. I hope to maintain that level because I believe such grants and the fruits of the research they support are the bedrock upon which our whole system rests and thrives.

I am well aware that my first priority implies another which in the long view is equally as critical--namely, the maintenance of adequate training programs. As a human enterprise, research has proved to be tremendously productive; and although we must be concerned with its financial support, its vigor is heavily dependent upon the continuous infusion of the efforts and ideas of young investigators.

If the surge into the unknown is to continue unabated, research institutions must accept the Hippocratic obligation "to implant this art by precept, by lecture and by every mode of teaching." For an agency like the NIH, that ancient injunction translates to providing predictable and adequate funding for research training. Through this means we can carry out our purpose to encourage and assist in the development of outstanding scientists and attracting the best young people into science. Of course, such training efforts must be reinforced by our assurance to young scientists that reasonably stable support will be available for the biomedical research to which they plan to devote their careers.

The nurture of basic research through supplying financial support and assuring the critical human resources is a concern of rheumatologists just as it is for every facet of medicine.

Because of my long-term involvement in medical education, I am also sensitive to the need to interest young physicians, nurses, and other health professionals in the challenges and satisfactions that abound in the field of rheumatology.

Just over a month ago, I participated in the Pan-American Conference on Health Research Policies held in Caracas, Venezuela. This meeting of the principal health officials of the countries of the Western Hemisphere was devoted to consideration of the optimum deployment of scientific resources for the improvement of health. We

discussed the selection of research priorities. The topic is highly relevant to this meeting as well.

While there, I expressed my conviction regarding the essentiality of basic research, just as I have on this occasion, noting that the great discoveries in biology and medicine have rarely if ever come from program planning by research managers. Rather, they have been achieved by individual scientists pursuing new leads as they have appeared, most often during research that was conducted without a specific application in mind. From this tenet follows the logical conclusion that it is important to assign the bulk of a large research budget to the support of investigator-initiated research.

Nevertheless, the research community cannot escape the challenging responsibility of planning for the application of basic knowledge to prevention, diagnosis, or treatment of specific diseases, the transfer into practice of new technologies, and the conduct of clinical trials of promising measures.

In the selection of priorities for applied research, we must assess the physical, emotional, societal, and financial burdens of various diseases; the readiness of the state of knowledge for application to disease prevention or treatment; and the potential impact of the various research strategies on reducing the burdens of disease. Even when reasonably accurate epidemiological data on a particular disease are available, they do not begin to describe its total burden. A sound assessment of research priorities beyond the basic stage must take into account the social and personal costs of a disease. In carrying out such evaluations, we need the insights and advice of persons outside the scientific and health professional communities. Each of the 15 or more policy level advisory bodies of the National Institutes of Health has substantial numbers of knowledgeable members from fields other than medicine and science whose perspectives reflect the broader social interest.

The various forms of arthritis and related diseases represent a set of difficult disease problems whose social and personal implications are far reaching indeed, and only in recent years has their magnitude been appreciated.

In 1974, the United States Congress formally recognized arthritis as a major public health problem having severe medical, social, psychological, and economic consequences. In the National Arthritis Act of 1974, the Congress called for a national plan for the best use and organization of national resources against arthritis and related diseases. It established a National Arthritis Advisory Board, charged to review and evaluate the implementation of the plan, and to make public an annual report on activities and

progress. Under the Board's charter, 6 of the 18 appointed members are members of the general public knowledgeable about arthritis.

One of the components of the NIH, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, was named in the 1974 Act as the primary Federal agency responsible for implementing features of the Arthritis plan and program.

Just a few weeks ago, an organizational change was effected by the Secretary of Health and Human Services, designating the NIADDK as a Bureau. This action permitted us to give further emphasis and visibility to the problems created by arthritis and to related research by the establishment of the Division of Arthritis and Musculoskeletal Disorders. Appropriately, the Division is headed by Dr. Shulman. Both the Pan-American Congress of Rheumatology and the National Institutes of Health have shown good taste and sound judgment in their selection of leaders.

Again, personally, and on behalf of the Government and the scientific community of your host country, I extend to you a most cordial welcome.

REMARKS*

by

James B. Wyngaarden, M.D.**

Secretary Schweiker, Dr. Brandt, Distinguished Guests, Colleagues, and Friends:

Mr. Secretary, I want to begin by thanking you for your kind and encouraging remarks and for the confidence you have shown in recommending me to the President to serve as the 12th Director of the National Institutes of Health. It is an immensely important and challenging position, and I pledge to you and to President Reagan to do my best in meeting its responsibilities.

I appreciate the presence of my family, my friends, and members of the NIH community who are at this ceremony, as well as of those who are watching by closed-circuit television.

I also want to express my thanks to Dr. Brandt for his help and wise counsel during the past few months. Valuable support has been extended to me by many members of the NIH community. I wish to recognize in particular Dr. Thomas Malone, who served as Acting Director, and Dr. Edward Rall, who served as Acting Deputy Director for Science. My admiration for their contributions grows daily as I begin to experience the demands of my office. We all owe them a debt of gratitude.

Secretary Schweiker has shown unusual interest in the programs and fortunes of this agency. I have been told that no other Secretary has known as much about or understood so fully the purposes of the NIH. He has repeatedly demonstrated his support for our activities, and his zest for learning more about what we do is welcome indeed. Just a few weeks ago, he came to the campus to have a first-hand look at the scientific programs of the National Cancer Institute and proved to be a challenging visitor. He plans similar meetings with other NIH Institutes and we look forward to these opportunities for interaction.

I have long had great respect for the NIH as the world's foremost institution in biomedical research. It is a precious national resource. My perspective is derived from

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*Formal Swearing-In Ceremony held in Masur Auditorium on June 21, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

years spent in research and education. I have been an intramural scientist at the NIH, a recipient of research and training grants supported extramurally by the NIH, and a member of NIH study sections, training comittees, and a Board of Scientific Counselors. These experiences have engendered a profound appreciation for the NIH intramural scientific program. This program permits an investigator to devote full time to research and to plan long-term studies with assured support. These advantages can be difficult to achieve in other settings. Opportunities for collaboration of basic and clinical scientists, and of investigators within or across disciplines, are especially congenial and fruitful here. In addition, NIH has been a training ground for hundreds of young investigators who have entered academic institutions and there have raised the standards of research and teaching. In many respects, the intramural research program at NIH stands as a quality control for the whole world of biomedical research. I am fully committed to maintaining the excellence and special attributes of this program.

I also wish to acknowlege the high quality of our extramural activities, and the essential role served by academic and other institutions that are supported through grants and contracts.

I am strongly committed to the pursuit of basic research as the foundation for the understanding, treatment, and prevention of disease and disability. I believe that investigator-initiated research holds the greatest promise for significant discoveries, whether it be conducted in NIH laboratories and clinics or at the 1,200 institutions receiving support from the NIH.

About 50 percent of the total NIH budget goes to grants for investigator-initiated research projects. I hope to maintain that proportion because I believe this part of our activity is the bedrock upon which the whole system is based.

I regard support for research training as inextricably linked to support of research itself. Clearly, if we are to have excellence and continuity in research, scientists must be trained to carry on this work in the future. Other aspects of our extramural efforts, such as the centers programs and clinical trials, must also be maintained if we are to fulfill our responsibilities. In addition, we will continue to emphasize prevention research and health promotion, two areas which have been declared by the Secretary to be special Departmental initiatives.

The NIH must seek to broaden and strengthen its long-standing partnership with academic and other scientific institutions. These are difficult times for universities and professional schools. We have a vital stake in their struggles as they cope with severe

financial stresses in order to maintain the quality and integrity of American higher education.

Our partnership must be a dynamic one, taking into account the inevitable changes in the life and growth of any institution. One such change is the emergence of industry as a partner in the biomedical research community. The NIH is ready to play its appropriate role in this growing relationship.

Last week I was pleased to announce three major appointments: Dr. Lester Salans as Director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; Dr. Mortimer Lipsett as Director of the National Institute of Child Health and Human Development; and Dr. Richard Crout as Associate Director for Medical Applications of Research. Today I am happy to announce a fourth appointment—that of Dr. Claude Lenfant as Director of the National Heart, Lung, and Blood Institute.

For all of us, I want to express to the several Acting Directors sincere appreciation for the way in which they have carried out their difficult assignments, some for extended periods of time. Their dedication and hard work have assured the continunity of vital programs without loss of momentum.

It is a great privilege for me to assume the Directorship of the NIH at this time in its history. Basic scientific knowledge in biology and medicine is expanding at an awesome rate—the stock of usable knowledge is at an all-time high and the opportunities for successful application of that knowlege to unsolved problems of health and disease have never been brighter. The next decade should see many exciting developments in science and medicine.

I firmly believe that future medical historians will conclude that the Golden Age of Medicine was not in the decades just past but in the years that lie immediately ahead. The NIH will continue to lead the way.

Thank you for honoring me with your presence this morning.

FIRST NATIONAL PUBLIC HEALTH SERVICE EQUAL EMPLOYMENT OPPORTUNITY CONFERENCE*

James B. Wyngaarden, M.D.**

Before introducing our distinguished keynote speaker this morning, I would like to summarize briefly my views on equal employment opportunity.

Since my recent appointment as Director of the National Institutes of Health, I have been briefed on our equal opportunity program. The goal of equality in all aspects of employment is an intergral part of the management and operation of NIH. We have a policy, a plan with objectives and an active division of Equal Opportunity to promote and monitor continued progress in this important area at NIH.

As for my personal view, let me put it this way: Scientific research advances only through complete freedom of inquiry and open exchange of knowledge. This means that there can be no arbitrary discrimination among those who seek to participate in the search for scientific knowledge. In fact, discrimination would mean denying the scientific endeavor of access to a rich source of talent and creativity.

As a scientist, I hold firmly to the principles of freedom, openness and opportunity for full participation by all. I intend to apply those principles in my administration of NIH and all of its activities. Equality of opportunity in employment is, and will continue to be, an integral part of all levels of activity at NIH.

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*Presented in the Sheraton International Conference Center, Reston, Virginia, on June 28, 1982.
**Director, National Institutes of Health, Bethesda, Maryland 20205.

Our keynote speaker today will expand on the topic of equal opportunity from the perspective of broad experience in government and industry. Our speaker drew on his formal education in science and law during a long career in public service and private industry.

An attorney and former Captain in the Marines, he joined the professional staff of the Joint Congressional Committee on Atomic Energy in 1952 and later served as Committee Staff Director. He participated in drafting the Atomic Energy Act of 1954 and joined Westinghouse Electric Corporation in 1956 at the Bettis Atomic Power Laboratory.

He took leave of absence in 1958 to serve as Special Consultant to the House Select Committee on Astronautics and Space Exploration and helped draft the National Aeronautics and Space Act.

He returned to Westinghouse where he was named Marketing Manager and Executive Assistant to the Vice President of the Atomic Power Division.

In 1962, our speaker accepted a Presidential appointment in the State Department and, in 1967, was appointed by the Atomic Energy Commission to serve on its Ad Hoc Advisory Panel on Safeguarding Special Nuclear Material. In 1970, he became a member of the Advisory Committee on Energy to the Secretary of the Interior and Chairman of the Nuclear Subcommittee.

An indication of the broader range of interests of our speaker is his service as Director of the American Nuclear Energy Council, the National Theater and the Washington Chapter of the National Epilepsy Foundation.

It is with pleasure that I present to you the Vice President for Government Affairs of Westinghouse, Mr. Francis P. Cotter.

OPENING REMARKS*

by

James B. Wyngaarden, M.D.**

It is a distinct pleasure for me to meet and welcome you to the first NIH Extramural Associates Workshop supported jointly by NIH and your institutions.

The Extramural Associates Program is the most recent addition to the other NIH minority programs, such as MBS (Minority Biomedical Support Program, DRR) and MARC (Minority Access to Research Careers Program, NIGMS). As distinguished from these and similar mainstay minority programs, the Extramural Associates Program starts at a point where the others leave off. That is, it builds on the scientific accomplishments of the other programs and, by focusing on the administrative aspects of science, provides an important transitional link to the mainstream biomedical research activities. In brief, the Program is a catalyst, and you are the conduit through which these catalytic reactions can take place.

I am pleased to note that your recent experiences on the Program parallel to a large extent those which I have recently undergone. I, too, have been taking a crash course on the countless issues that require the attention of the Director of NIH, and you, on the research programs of the NIH, the support mechanisms through which this research is being accomplished, and the policies and procedures that govern the awarding of grants and contracts.

I also consider it very important that you have had the opportunity to become a part of the NIH family. Henceforth you are the links between your community and the Federal establishment by providing the "insider's" point of view. But an "insider's" view needs continuous updating and reorientation.

Unchangeable for NIH is its tradition of excellence in research and service to humanity. My primary aim will be to maintain and enhance that tradition.

This is a critical period for NIH and the field of biomedical research. The explosion of biomedical knowledge and improved technology in recent years offers

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*Presented at the NIH Extramural Associates Program Workshop, Bethesda Marriott Hotel, on June 30, 1982.

**Director, National Institutes of Health.

greater opportunity for advances in medicine and health than ever before. At the same time, we must deal with the reality of economic constraints.

I am heartened that the key officials in the Administration as well as in the Congress recognize basic research as the foundation for the understanding, treatment, and prevention of disease and disability. I am strongly committed to that view and believe that investigator-initiated research holds the greatest promise for significant discoveries. As you know, half of the total budget of the NIH is allocated to the support of investigator-initiated research projects. I shall continue to support that approach to doing research.

I further regard the support for research training to be inextricably linked to the support of research itself. Clearly, if we are to have excellence and continuity in research, scientists must be trained to carry on this work in the future.

Other aspects of our extramural efforts—such as the Centers Programs and Clinical Trials—must also be maintained, because they are essential elements in a comprehensive program of biomedical research. In addition, we will continue to emphasize prevention research and health promotion, two areas which have been declared by the Secretary to be Special Departmental Initiatives.

Finally, we shall continue to ensure that there are ample opportunities for new and developing scientists, including those from racial and ethnic minority groups and women, to join and contribute to the mainstream of biomedical research. We expect that the Extramural Associates Program, and particularly this workshop, will help us have a special impact in this direction.

Best of luck to you in your endeavors.

WELCOME TO EUROPEAN ORGANIZATION FOR CARIES RESEARCH (ORCA)

James B. Wyngaarden, Director,
National Institutes of Health
June 30, 1982

I am delighted to welcome the members and guests of the European Organization for Caries Research to the United States and to Washington.

We are especially honored by the decision of this prestigious international organization to come to this country in recognition of one of the research programs of the National Institutes of Health.

Since the establishment of the National Institute of Dental Research some 34 years ago, the NIH has been strongly committed to research into the causes and prevention of dental caries which continues to be a disease of major concern in the United States. Out of this concern, and to provide a focus for research activities, the National Caries Program was launched just over 10 years ago. During this decade, the program has made substantial progress toward the eventual control of caries.

We are also actively interested in promoting strong ties with research groups and scientists in other countries working on health problems of mutual concern. Because of this interest in international joint efforts, the continuing close collaboration of ORCA and NIH scientists is especially gratifying. We hope this

collaboration will continue and are confident that through such sharing of knowledge and efforts, the pace of research will be accelerated to the benefit of people everywhere.

I am not only gratified by this meeting as evidence of a close and productive partnership but, as a scientist, I am impressed by the variety of the scientific areas to be discussed during the 29th Congress of ORCA.

I am sure that the Congress will prove to be a successful one and will contribute significantly to the prevention of dental caries.

I wish you all a most pleasant evening and an enjoyable and profitable time as you meet in Annapolis.

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FOR RELEASE UPON DELIVERY

STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

JULY 20, 1982

Mr. Chairman and Members of the Committee:

Thank you for the opportunity to comment on S. 1939, a bill to establish a National Institute of Arthritis and Musculoskeletal Diseases at the National Institutes of Health. The legislation proposes, among other things, to transfer arthritis programs and activities from the present National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) in order to create the new institute.

I have two major objectives in my testimony, Mr. Chairman. The first is to speak in opposition to the creation of a National Arthritis Institute at this time. The second is to speak to a larger issue of which this proposal is a part, namely the recurring calls for the creation of additional, categorical, or disease-specific Institutes at the NIH where we now have 11 such Institutes.

In calling the attention of the Committee to what I perceive to be the dangers of this movement for additional Institutes, I do not wish to impugn in any way the motives of those who recommend this course of action. There is a perception among the public and also among many voluntary health agencies that the way to accelerate progress in the understanding, treatment, cure, and prevention of a particular disease is to organize the research in that disease into a separate institute. Mr. Chairman, I believe such well-intentioned proposals rest upon an erroneous conception of how biomedical research actually functions most effectively.

Biomedical research today tends toward a focus on the cellular and molecular origins of disease, on the discovery of unifying concepts of the life process itself. Discoveries in one field of basic biological science may lead to breakthroughs in the treatment or prevention of human disease in some quite unforeseen disease category. Such basic biomedical research takes place in all the NIH Institutes. Its pace is a function of scientific opportunity and available funds and the creative insight of the scientist, not of the number or names of the Institutes.

An apt comment on the importance of basic research comes from Irving Langmuir, a Nobelist in chemistry, who said: "Only a small part of scientific progress has resulted from a planned search for specific objectives. A much more important part has been made possible by the freedom of the scientist to follow his own curiosity in search of truth."

Later in this statement I will cite examples of how cross-fertilization of scientific ideas has contributed to the therapeutic progress against specific diseases. I will also offer some suggestions as to how we might approach the broad issue of management of the biomedical research enterprise.

Administration Position on S. 1939

Turning first to S. 1939, I want to emphasize that while we understand the goals of the legislation to create a separate Arthritis Institute, Mr. Chairman, we must respectfully oppose the proposal as counter-productive on scientific, managerial, and fiscal grounds. We believe the objectives of the proposed new Institute are already being actively and capably pursued by

the present NIADDK. Arthritis and musculoskeletal diseases are already receiving a very high level of research priority within NIH, as they should. This group of arthritic disorders, which affect some 37 million Americans and cripple some 5 million, warrants our urgent attention. Such an emphasis is being directed at these maladies within our present resources and structure.

Arthritis-related research is conducted through several Institutes at NIH, in addition to that in NIADDK. In fact, about 25 percent of this work takes place in the Allergy and Infectious Disease, Cancer, Heart, Dental, Aging, and General Medical Sciences Institutes. The location of the largest programs in arthritis research in NIADDK creates the cross-fertilization of ideas and technologies through the close integration of arthritis research with related disciplines. Progress in arthritis-related research requires a greater understanding of genetics, metabolism, immunology, endocrinology, and nutrition.

I might mention at this point, Mr. Chairman, my personal interest in this subject. For some 30 years, I have been involved in arthritis-related research. In the early 1950's as a scientist in the National Institute of Arthritis and Metabolic Diseases, I worked on the chemical transformation of cortisone and other steroids in normal and arthritic subjects. My major research interest over more recent years has been the role of purine and uric acid metabolism in gouty arthritis. At the Duke University School of Medicine, I was in charge of the arthritis research training program from 1960 until just this spring when I returned to the NIH. It is with that kind of background that I approach the question before us today.

Scientific Considerations

I should point out, Mr. Chairman, that the term "arthritis" refers to a broad family of more than 100 rheumatic and related disorders of the joints and connective tissues. Some disorders that produce arthritis involve not only the musculoskeletal system, but the blood vessels, kidneys, lungs, skin, eyes, and brain as well.

Because so many different systems of the body may be involved in these diseases, the arthritis and musculoskeletal disease area currently derives significant advantages from its close association with other areas of NIADDK through the sharing of basic biomedical research approaches and disciplines. Let me cite a few examples of the interrelatedness of programs in the field of arthritis and musculoskeletal diseases.

Systemic lupus erythematosus, abbreviated as SLE, is a relatively common disease that can affect many organs and is, therefore, under study throughout NIADDK as well as in the Allergy, Cancer, and Heart Institutes. Lupus nephritis affects the kidney and is the most serious manifestation of this disease. It is of special concern to the kidney program within NIADDK. Lupus also involves the skin and hair. These manifestations are of special concern to the skin program of NIADDK. Steroid treatment of lupus involves the metabolism and diabetes programs. Blood-clotting abnormalities of lupus are studied by scientists in the hematology and nutrition programs.

Osteoporosis is a disorder of bone metabolism found in several forms of arthritis. It also occurs independently. It is a major concern of the

metabolism program within NIADDK and is also studied in several other Institutes such as those for Aging, Dental Research, Child Health, and General Medical Sciences.

The role of infection, by viruses or bacteria, is another important area of study in many forms of arthritis. It has long been known that infections by such bacteria as staphylococcus and gonococcus can lead to joint inflammation. A new disease, Lyme arthritis, was discovered in 1976 and traced to a tick bite and a spirochete infection. It is being examined as a model for the study of infection as an initiator of arthritis. Recent research shows that antibiotic treatment can lessen or prevent the symptoms of this disorder. The Lyme arthritis research is sponsored by NIADDK and the National Institute of Allergy and Infectious Diseases (NIAID).

The kind of work illustrated by lupus erythematosus, osteoporosis, and Lyme arthritis, but applicable more generally, benefits from the collaborative research climate that now prevails at NIADDK and across NIH, but it might not be as effective in a more narrowly defined and separate structure. There is the possibility that, through separation, research efforts may be isolated, even duplicative, and that biological interrelationships may not be explored fully. In a complex disease area like arthritis, Mr. Chairman, basic research is essential and, in that endeavor, cross-feeding and interchange of ideas must be encouraged.

It would be very damaging to many other programs of NIADDK and NIH if all of these research endeavors relevant to arthritis were collected into one

institute. Conversely, there is no special merit in establishing a new institute to promote the study of arthritis unless substantially greater resources were to be provided. And when the economy improves, increased funds for arthritis research would be more effective if the arthritis and musculoskeletal program remained integrated with others of NIADDK, and if new funds could be applied to basic science areas of greatest scientific opportunity.

New Management Initiatives

I mentioned earlier that NIADDK is pursuing the objectives of the proponents of the new arthritis institute actively and capably at present. Let me expand on that statement.

First, as you know, Dr. Lester B. Salans, a highly regarded scientist and experienced administrator, was recently named Director of NIADDK. Dr. Salans has been with NIADDK since 1976 and has served as acting director since last October so there will be no need for a "startup" period in his administration of the Institute's research programs.

In recognition of the importance of research into arthritis and musculoskeletal diseases, Secretary Schweiker last April 22 elevated NIADDK to the level of Bureau of the Public Health Service. In so doing, the Secretary created a separate Division of Arthritis, Musculoskeletal and Skin Diseases within the Bureau. This will greatly increase the visibility and stature of research into arthritis and musculoskeletal diseases, while maintaining the close interrelationship among research efforts within NIADDK.

With this new Bureau status and Dr. Salans at the helm of NIADDK, Mr. Chairman, I can assure you that the arthritis research program will be pursued vigorously. For example, the Institute has begun a comprehensive program of management initiatives, including the following:

- Stronger roles for the Division Directors, in order to achieve greater autonomy, independence, and public visibility for the Divisions.
- Identification of research projects that cut across categorical disease areas and are common to more than one program, in order to integrate and coordinate more closely support of related research.
- Implementation of remaining major facets of the National Arthritis Plan, the National Diabetes Plan, and the National Digestive Diseases Plan.
- Development of a new system for allocating funds among the Institute's programs.
- Improvement of working relationships with professional and lay groups with an interest in NIADDK, including strengthening the role of the NIADDK National Advisory Council, and increased involvement with, and support of, the activities of the National Advisory Boards for Arthritis, Diabetes, and Digestive Diseases.

Even before these management initiatives were launched, significant emphasis was placed on research into arthritis and musculoskeletal diseases. To illustrate, I would like to call the Committee's attention to a table and two graphs concerning NIADDK support for research in this area between 1976 and 1981.

The table shows that during the past five years, funding for research related to arthritis and musculoskeletal diseases increased from approximately $27 million in 1976 to more than $61 million in 1981.

The first graph shows the extent of growth of the Arthritis and Musculoskeletal (AMS) program during the past five years, compared with both the total NIADDK and total NIH programs. The same dramatic increase is found when one looks at the ten-year period, 1971-81.

The second graph compares the arthritis and musculoskeletal and skin diseases research program with the other three research clusters within NIADDK, Diabetes, Endocrinology, and Metabolic Diseases (DEM); Kidney, Urologic, and Hematologic Diseases (KUH); and Digestive Diseases and Nutrition (DDN).

As you can see, Mr. Chairman, whether compared with NIADDK, with NIH as a whole, or with the other research clusters, it is clear that arthritis and musculoskeletal disease research has been effectively promoted in recent years.

Priority support of this kind, along with new management emphasis in the arthritis area will, I am confident, build on research advances of the past five years. Among these are the following:

- Improvement in techniques for joint replacement, especially artificial hips;

- Evidence that some forms of arthritis apparently involve a genetic predisposition which may be "triggered" by environmental factors;
- Development of new arthritis drugs, based on knowledge gained from basic and clinical studies;
- Greater understanding of immune mechanisms responsible for some forms of arthritis and their potential for specific therapeutic intervention;
- Greater understanding of the inflammatory process and potential for therapeutic intervention.

I suggest, Mr. Chairman, that this kind of investment and achievement in arthritis research demonstrates that this effort is well served within the framework of NIADDK. I can assure you that there will be no lessening of that effort in the future.

Fiscal Considerations

Mr. Chairman, the creation of a new Institute would require substantial additional expenditures and personnel. Personnel would be needed to staff the administrative offices of a new institute, including extramural program management, direct operations, and the administration of intramural research. These positions would need to be taken from elsewhere in NIH, thus draining the resources of other Institutes.

We estimate that the cost of extramural program management, direct operations, and the administrative portion of the intramural research program for a new Institute would total approximately $5 million in the first year alone. Like personnel, funds to support the administrative costs of a new

institute must be found by cutting back in other areas. We would have to reduce direct research activities in order to pay the administrative costs necessary to set up a new institute.

The cost estimates are based on the average administrative requirements for an institute of the size being contemplated. They also incorporate the administrative experience of NIADDK which, incidentally, reports the second lowest administrative costs of the 11 Institutes at NIH.

These cost estimates are conservative, Mr. Chairman. But we have prepared them with the concept of a vigorous and dynamic Arthritis Institute in mind, which we assume is a major objective of the proponents of this legislation. The personnel estimates reflect that concept. The estimates would move higher if an expanded role was assigned to the new Institute.

At a time when we are all asked to be prudent financial managers, expenditure of approximately $5 million in additional funds for administration would erode already limited funding for basic and clinical research in the extramural and intramural programs of the NIADDK as a whole and, more to the point, in arthritis-related research as well.

For example, in the area of investigator-initiated research projects--the foundation of our basic research program--we project support for 126 new and competing grants under the President's fiscal 1983 budget for the Arthritis, Musculoskeletal and Skin Diseases Division. If additional funds were not newly appropriated, establishment of a new institute would mean that funding

for some 40 of these projects may need to be diverted to new administrative and operating costs. That would amount to a reduction by one-third of the competing grants in the AMS research area.

For these reasons--scientific, managerial, and fiscal--we believe it would not be in the best interest of our research programs to establish a separate Arthritis Institute at this time. I suggest that we should be investing in research, not institutes.

A Broader Perspective

I would like to return now to the broader issue mentioned earlier, namely, the question of additional categorical, disease-specific Institutes at NIH. Through the years, concern over various disease and organ systems has prompted the Congress to establish new Institutes at NIH.

Given the many still unsolved disease entities, and their serious threats to health and well-being, there is virtually no end to the possibilities for creation of additional categorical Institutes. There are many arguments for and against this organizational approach to the nation's biomedical research effort.

There is no question that this approach has been highly successful in the past. But I believe we are at a stage in the development of biomedical knowledge, and of NIH, when it is appropriate to take a close analytical look at the structure of the research endeavor and its management. The basic

question is: How best can we maintain our momentum and achieve maximum benefit from our research investment?

From a scientific viewpoint, Mr. Chairman, it may be wise to examine the categorical, disease-oriented structure of NIH. Modern biomedical research focuses increasingly on the underlying processes of sickness and health, less so on the symptoms of specific disease entities. It is from such deeper understanding of the life processes that we can expect the most important preventive and therapeutic achievements in the years ahead.

From the fiscal and managerial point of view, we are faced with the question of whether organizational complexity tends to be counterproductive. At present, for example, 29 senior officers of organizational units within NIH report to the Director; there are 16 separate budgets to develop and manage each year.

Questions concerning NIH organizations have arisen repeatedly in the past, but they seem to be more urgent today. The situation was summarized just five years ago by the President's Biomedical Research Panel which said, after a comprehensive study, that the categorical organization of NIH has created two challenges to management: "(1) an ever-increasing span of control for the Director, NIH, and (2) a need to assure that this structure does not inhibit interdisciplinary research at a time when all aspects of research, whether fundamental or applied, are increasingly interrelated." The Panel concluded that:

". . .the creation of additional Institutes is not likely to make the NIH more effective; it might well make it less so. Therefore, if new programs are to be established, or existing programs strengthened, this should be accomplished through the present Institutes rather than through the creation of new ones."

Mr. Chairman, I believe we are at a stage of development when another careful review of the NIH organizational pattern is in order.

Pending now before the House is a proposal for such an evaluation. It calls for a study by the Institute of Medicine, a component of the National Academy of Sciences, which would review the effectiveness of the existing combinations of disease research programs within the individual national research Institutes and of the criteria which should be followed in establishing new or realigning existing national research institutes. Secretary Schweiker has expressed his support of such a study. I agree that such an evaluation would be timely and hope that the Committee might take the subject under consideration.

In conclusion, I should inform the Committee that the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council expressed opposition to creation of a new Arthritis Institute at this time, and the National Arthritis Advisory Board did not express support for the concept of a new institute at its recent meeting.

Many health and professional organizations have expressed concern over creation of an Arthritis Institute and its likely impact on proliferation of categorical institutes. They include: The American Federation for Clinical Research, the American Medical Association, The Federation of American Societies for Experimental Biology, the American Society of Hematology, Cooley's Anemia Foundation, the Association of American Medical Colleges, the National Academy of Sciences, and the American Kidney Foundation.

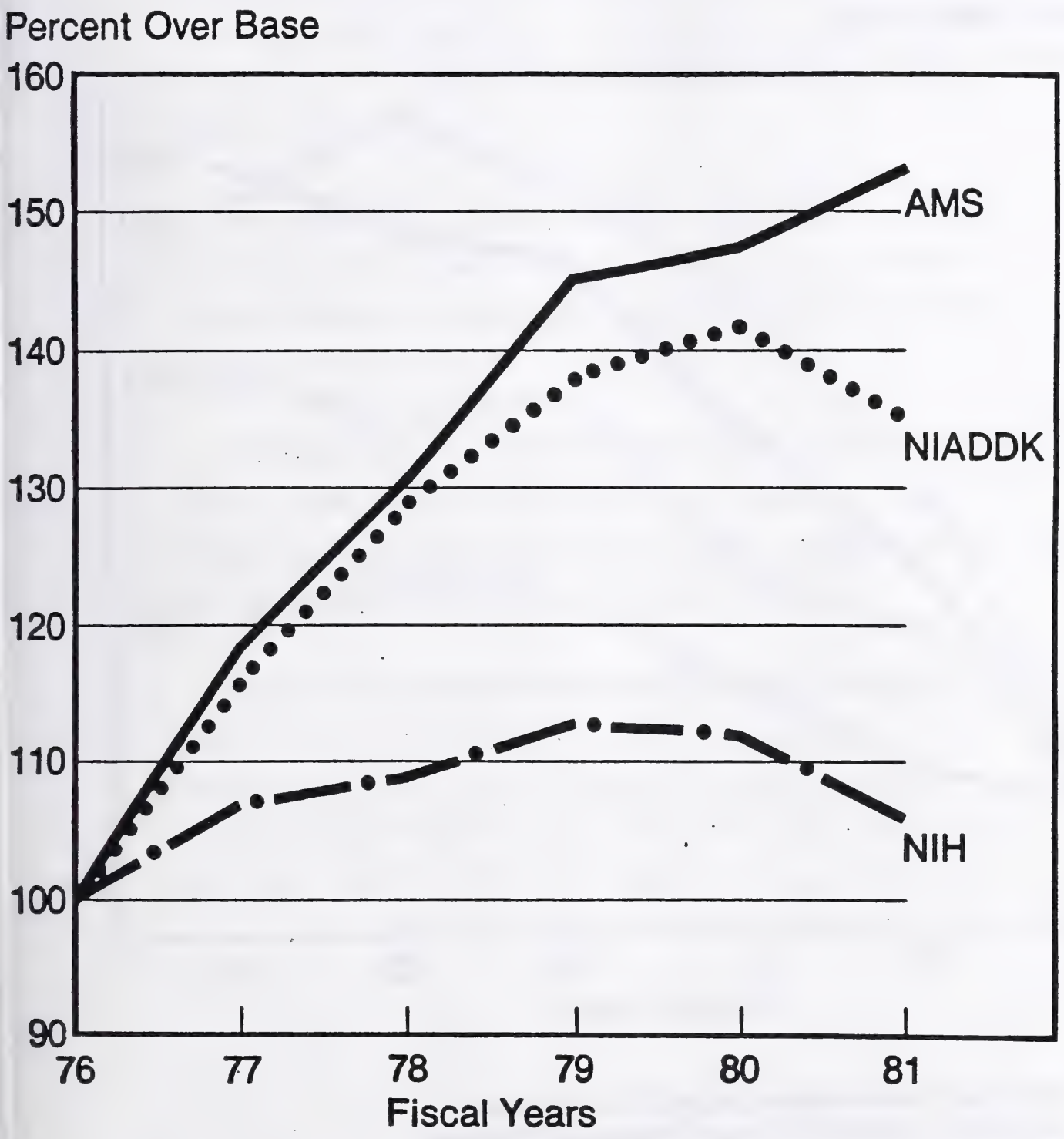
I hope, Mr. Chairman, that the Committee will support our position opposed to the creation of an Arthritis Institute at this time. Further, I hope the Committee will endorse a proposal for a study of the structure of NIH and defer consideration of an arthritis or any other new institute until that study is completed.

I will be pleased to answer any questions the Committee might have.

Budgets of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
(In thousands of dollars)

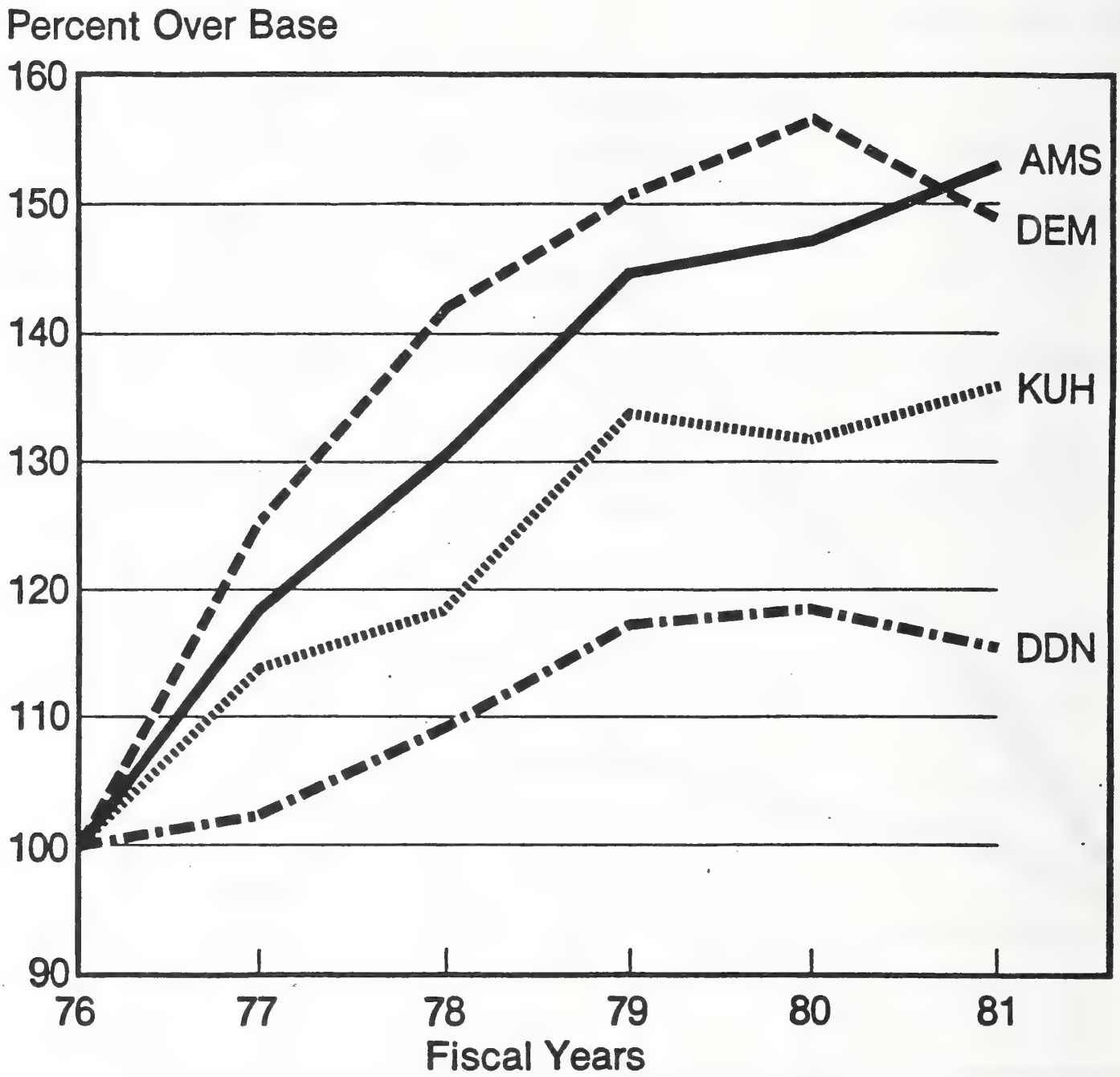
Fiscal Year	Arthritis and Related Diseases	Musculoskeletal Diseases	Total
1976	$18,602	$ 8,433	$27,035
1979	35,091	13,113	48,204
1981	44,794	16,936	61,730

Percent Change in Total Program Over 1976 Base
(in constant dollars)



AMS — Arthritis, Musculoskeletal and Skin Diseases

Percent Change in Total Program Over 1976 Base
(in constant dollars)



AMS — Arthritis, Musculoskeletal and Skin Diseases
DEM — Diabetes, Endocrinology and Metabolic Diseases
UH — Kidney, Urologic and Hematologic Diseases
DDN — Digestive Diseases and Nutrition

DRAFT

Remarks by Dr. Wyngaarden

OD Summer Employee Awards Presentation
Thursday, August 19, 10:00 a.m.
Wilson Hall

It is a pleasure to welcome you today--to affirm the importance of this special summer program at NIH, to thank all of the participants for their work here this year, and to honor those who have earned special recognition.

This small group is representative of a program that has offered opportunity to many throughout NIH for the past 13 years. My remarks to this first assembly of those who work as members of the OD family extend to your counterparts in all of NIH.

This time of year--with its hint of fall in the air--is special to me, having spent most of my life in an academic community. In that setting, the new year begins in September. There is a feeling then of anticipation of new experiences, of learning new things.

I hope you look forward to the new year with that same expectation--and that you take with you a broader perspective because of your experience here. The spirit is renewed by fresh ideas expressed by people with many interests in a place where knowledge and understanding are prized. To my mind, NIH is such a place. I hope you found it so.

There are many brilliant scientists here, doing important work. Some of the research is so advanced that only a few can understand it fully. But, everyone can understand its purpose: the conquest of disease and disability; better health for all.

By working here, I'm sure you learned that such a mission is not achieved in isolation; a community of many talents and abilities is necessary. Everyone helps to move us toward our objectives. Your work contributed to that common effort.

Your brief encounters here--with our ideas, people and mission--will serve as a sample of similar experiences to come. As you return to school or pursue careers, and face new and more difficult challenges, remember your NIH experience. There will always be opportunties to learn, to enrich your lives and to play an important role in a larger enterprise. There are no limits, only barriers to overcome, problems to solve. The important thing is to be open to ideas and be prepared to seize opportunity.

I want to congratulate you and express our thanks for the initiative and diligence that brought your work to the attention of co-workers and supervisors. Special effort deserves special recognition and I am pleased to take part in this ceremony in your honor.

I hope that some of you have been encouraged here to seek careers in science or in some part of the vast health care enterprise which needs good people. Perhaps we will welcome some of you in careers here at NIH.

I won't wish you luck this morning because I am confident that you will make your own. But I do congratulate you and extend my best wishes for success and satisfaction in the future.

OFFICE OF THE DIRECTOR
SUMMER EMPLOYEE
AWARDS PRESENTATION

Thursday, August 19, 1982

10:00 a.m.

Wilson Hall, Building 1

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Master of Ceremony	Mr. Otis Ducker, Director Division of Administrative Services
Keynote Speaker	Dr. James B. Wyngaarden Director, NIH
Student Speakers	Cynthia Webb, OPPE Derek Griffin, DAS Sarah East, DCG
Presentation of Awards	Dr. Philip S. Chen, Jr. Acting Deputy Director for Science, NIH
	Helen C. Stafford Assistant Director for Operations, DPM
Closing Remarks	Mr. Otis Ducker

OFFICE OF THE DIRECTOR
SUMMER AWARDEES

Donnell Adams
Wendell Anderson
Mara Bluebond
Renee Brooks
Lisa Carter
Ronnie Carter
Raphael Chandler
Ronald Coleman
Kenneth Compart
Melvin Graves
Barbara Guariglia
Evelyn Hardy
Linda Hipp
Beverly Jackson
Wainwright Jackson
Andrea James
Aretha Johns
Michael Johnson
Marcus McCombs
Wilma Middleton
Robert Nolte
Cheryl Parker
Heinrich Rosser
Michael Roy
Wayne Scales
Marcia Slaughter
Arnita Smith
Mark Smith
David Snow
Beverly Tibbs
Donnell Thomas
Kitti Virts
Victoria Ward
Cynthia Webb
Ronald West
Robert Whaley
Jane White
Columbus Williams
Felicia Wilson
Trisha Wilson
Susan Woolley

Group Award

Nathan Bagby
Dennis Barnes
Pamela Coleman
Geoffrey DeLaine
Roslyn Mickens
Angela Milhouse
Willie Murphy
Lorna Sharpe

Academic Science and the Federal Government in the 1980s*

by

James B. Wyngaarden, M.D.**

When I first saw the topic of today's symposium, "Academic Science and the Federal Government in the 1980s," I began mentally to sketch paragraphs on "indirect costs," "stabilization," "investigator-initiated research," "contracts," "centers," "patents," "small business set-asides," "new institutes," "obsolete equipment" and other equally difficult subjects that have displaced those things I used to think about before coming to the NIH this Spring. But instead of focusing on such details, I have decided to offer some comments on broader aspects of the Federal-academic partnership that has been so productive in the realm of biomedical and behavioral research.

From the perspective of the health sciences and biomedical research, the active partnership of the Federal Government and academic science began in 1940. In the summer of that year, the Surgeons General of the military services called upon the National Research Council for advice in many fields of medicine and surgery. The following year, the Committee on Medical Research was organized under the Office of Scientific Research and Development to "initiate and support scientific research on medical problems affecting the national defense." By December of 1944, the Committee had executed almost 500 contracts for medical

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*Presented at American Psychological Association Symposium, Washington Hilton Hotel, on August 26, 1982.

**Director, National Institutes of Health, Bethesda, Md.

research at 120 different institutions. Over 95 percent of these research contracts were with universities or teaching hospitals.[1]

Forty years later, as we enter the fifth decade of the federal-academic partnership in biomedical research, one can take a degree of encouragement in making predictions for the 1980s from the fact that the basic principles shaping that partnership have changed very little since the years immediately after World War II. Furthermore, a number of issues for the '80s--what to do about obsolescent equipment and instruments, patents, overhead, rising costs, small business, stabilization--were recognized as questions in the forties.

In a report written in 1945 titled "Science - The Endless Frontier," Dr. Vannevar Bush, the President's Science Advisor, outlined the policies for Federal support of health research that have served the national interest so well in the succeeding years. The flavor and substance of the document stand up well when viewed from the perspective of nearly 40 years. Permit me to read a few sentences from it:

"The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. . ."[2]

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[1] Science-The Endless Frontier, p. 47.

[2] Science-The Endless Frontier, p. 7.

"While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any extension of medical facilities must be accompanied by an expansion of medical training and research."[3]

"Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."[3]

At the heart of the policy considerations of the forties was the conviction that the limiting factor in the future of science is a human one. As we contemplate the '80s, the central challenge is unchanged: How do we assure a continuing renewal of the body of first-class scientists who can and will put their creative energies to the search?

Happily, our national consideration of that question has been more realistic than it was in a situation mentioned by Jacques Barzun in his book "The House of Intellect." "It is said," Barzun wrote, "that in Rydal Mount, where Wordsworth lived, the peasants speculated among themselves whether the poet's son would carry on the business of poetry when the old man died." [4]

Most of the issues at the top of the '80s list are subsidiary to the concern that somehow we must make careers in research attractive and feasible for the best of the generation now setting the course for their careers.

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[3] Science-The Endless Frontier, p. 9

[4] The House of Intellect, p. 210

A 1977 statement titled "Research Universities and the National Interest," and authored jointly by the presidents of 15 major universities, addressed this point. They noted that "First-rate work in any field of human action is rare and difficult, but nowhere is the quality of work more decisive than in higher learning and research....In the simple words of Philip Handler, [the recent] President of the National Academy of Sciences, 'In science the best is vastly more important than the next best.'"[5]

How do we signal to the young investigator in a time of budget constraints that research careers are not restricted to the very few and, in doing so, how do we avoid a dilution of support that could seriously weaken the scientific effort?

Through the years, NIH has relied on the investigator-initiated project grant as its prime mechanism for the support of biomedical research. Almost exactly 50 percent of our $3.6 billion budget for 1982 will be used to fund about 15,000 such grants. The term of the average grant is something over three years, so that each year between one-fourth and one-third of our grants are either new or competitive renewals of existing grants.

Our efforts at "stabilization" have focused on assuring that a predictable and substantial number of such grants can be made each year. The Stabilization strategy is based on our experience that over half of our new project grants,

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[5] Research Universities and the National Interest, p. 5

amounting to about 12 percent of all grants, are made each year to first-time principal investigators. Responsibility for the future productivity of the research enterprise rests heavily on these newcomers, and somehow the door must be kept open for them without jeopardizing continued support for investigators who are in their prime years of creativity. Another and equally important facet of Stabilization is to maintain research training programs at predictable levels. While the NIH supports only a fraction of the individuals in research training, it is an essential fraction needed to assure the replenishment of a critical mass of first-rate scientists.

Some have urged the NIH to spread its funds over a larger number of investigators by funding many projects at levels well below the amounts recommended by peer reviewers. A widely expressed version of this concept would apply a sliding scale to the amounts awarded for projects on the basis of the technical merit ratings given them by our study sections.

A mechanistic application of the sliding scale principle would represent a major change in the long-standing NIH policy of awarding grants on the basis of scientific merit and program relevance. Such a practice would negate the considered judgment of the study sections as to adequacy of the budget of a research proposal. It would ignore the strong probability that there is a critical quantum below which many projects would become an ineffective waste of funds. Although we share the desire to fund the largest number of investigators possible, we continue to feel that this must be done without departing from the criteria of scientific merit and program relevance. The question brings to mind John Gardner's query, "How can we be equal and excellent too?"

The development of the NIH budget for 1983 provides an illustration of the fiscal dynamics and dilemmas of the early '80s. In order to make more funds available for the support of new research, the NIH has proposed among other adjustments a plan to fund indirect costs on all grants at only 90 percent of the negotiated rate. This proposal now constitutes ~~as~~ a part of the President's budget for NIH in FY 1983 which is presently before the Congress. Although greeted generally with applause from scientists, this proposal has engendered a concerted, vigorous and uniformly negative response from administrators of grantee institutions who look upon it as an arbitrary and unilateral abrogation of established principles. The loss of indirect expense funds exacerbates the financial distress that already besets many of our academic partners.

In our on-going discussions of this matter, we do not dispute the fact that indirect costs are real. We are concerned, however, that there has been a steady increase in indirect expenses of research from about 15 percent of the total research award in 1966 to the current 29.5 percent. At issue is the extent of cost sharing of the overhead of research by the university in return for the general strengthening of the university through the research support received from the Government.

The NIH did not intend this 10 percent reduction in funding of indirect costs as a permanent measure. It was proposed in order to distribute budgetary restraints across both research and overhead activities during FY 1983 and as a signal that indirect costs funded by the Government needed to be contained and perhaps reassessed as to their appropriateness as a charge to the Government.

Another issue that concerns me is the extent to which faculty salaries consume the research dollar. When Vannevar Bush and his colleagues charted the Federal entry into research collaboration with academia, they emphasized the importance of the intact institution serving the traditional goals of a university. They could foresee the pressures of divided loyalty experienced by a research investigator whose base is in a university but whose support is Federal funds. Today's pattern of faculty support from Federal granting agencies evolved in steps: First, there was the summer salary for the faculty member who was on a regular nine-month appointment; then came reimbursement for released time so that the institution could "fill in" for the investigator who was working on a research project; and finally came full reimbursement to the faculty member for all time spent in research activities. The extensive use of grant funds for the salary support of tenured faculty seems to carry the implication that research is an extraneous activity rather than a part of the fabric of the academic life. We will be exploring alternative mechanisms of faculty support through the university that might strengthen rather than weaken institutional loyalties.

Faculty members in academic medical centers are especially vulnerable to the centrifugal forces generated by the various sources of funding on which such centers must depend. Income from patient care and funds granted for research by the Federal Government have been and will continue to be major variables in the financial equation of medical centers. Of late, large research grants from industry, along with lucrative consultancies and corporate memberships, have entered the financial picture for faculty scientists. Such arrangements can be

of benefit to all concerned, but they also may carry with them a threat to freedom of inquiry and the right to publish, and the possibility of creating conflicts of interest or further conflicts of loyalty.

One of the challenges will be to assure that institutions and their faculties are not diverted from their traditional commitments to teaching and research, and that the kind of structural integrity which has been so important to the growth of the American educational institutions is not weakened by fragmentation.

The "Report of the Fifteen Presidents" contained a warning about the Federal/academic relationship. They cautioned "The greatest single danger before the world of education, in its relations with the Government, is that it may divide against itself . . ."[6]

That general warning deserves attention from all of us who believe in the productivity of the Federal/academic partnership in research, especially at a time when we will be required to adjust and readjust to financial uncertainty. Together, American academic institutions and the Federal Government have been responsible for creation of a research enterprise in the biomedical and behavioral sciences whose benefits for the Nation have been incalculable. The prospect for even greater accomplishment in the '80s is bright. Although a long period of acceleration with increased Federal support came to a temporary halt in the late '70s, the momentum is massive when measured in terms of promising ideas and the numbers of trained scientists eager to exploit the new leads.

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[6] Research Universities and the National Interest, Preface p. v

But the pause in growth--actually a decline in real dollars since 1979--has frustrated many applicants for new or continuation grants, and has, perhaps understandably, provoked some vigorous efforts to change agency policies or reorder agency budgets. We see instances of disappointed applicants striking out at the peer review system, attacking its validity and equity. Some groups have promoted the enactment of special program authorizations in order to by-pass the rigors of peer review. Occasionally, members of Congress call to inquire why we have not approved a constituent's grant application of which the Congressman has received a copy even before ours has arrived. It is my hope that the scientific community will work to support and strengthen, and not to subvert or circumvent the peer review system. It continues to be the fairest and most competent mechanism available to assist research administrators in the evaluation of research proposals.

There is no reason to believe that the Federal/academic partnership is dissolving or that progress in research is about to stop in its tracks. We have ample warning, however, that our commitment to the principles that have served so well in the past may be tested in the coming decade. We plan to consult widely with the academic sector, including both its administration and its scientists, as we probe for more effective policies appropriate to the constraints of the '80s.

# # #

REMARKS: NICHD 20th ANNIVERSARY COMMEMORATION*

By

James B. Wyngaarden, M.D.**

Although we are meeting in the fall of the year, I sense a feeling of commencement as we observe the 20th anniversary of the National Institute of Child Health and Human Development. The past two decades have seen a remarkable outburst of discovery in biomedical research. We are, as has been noted, ready to capitalize on the findings of the "biological revolution." Scientific researchers have reached the root causes of disease and disability, the cellular and molecular level of the life processes. Now, throughout the National Institutes of Health and the biomedical research community at large, there is a sense of expectation, of the nearness of answers to age-old questions.

That sort of feeling is especially appropriate at this Institute which has the specific mission of exploring the fundamentals of human development. The more we learn about the very beginning of life, the better able we will be to maintain health and overcome the maladies of the latter years. This Instsitute has made many contributions to knowledge and to better health over the past 20 years through the study of the defects and disorders of birth and development. But, in the long run, I think the major contributions will be seen to have arisen from the meticulous study of what is normal--through the understanding of what is normal, we can eventually overcome the abnormal.

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*Presented at the 58th Meeting of the National Advisory Child Health and Human Develoment Council held on September 20, 1982, at 8:30 a.m. in Wilson Hall, Building 1, National Institutes of Health, Bethesda, Maryland 20205.

**Director, National Institutes of Heath

Because it is given a broad mission, the establishment of NICHD broke new ground in the organization of the research endeavor at NIH. The Institute's charter recognized the unity within the complexity of the life process. That was a break from the disease-specific orientation of the earlier Institutes. As we pursue biomedical research into the next century, I believe there will be increased recognition that fundamental studies are the key to the conquest of a broad array of seemingly disconnected disorders. In practice, of course, a cross-feeding of knowledge and an interdisciplinary approach is common among biomedical investigators. In fact, there is growing interchange within the biomedical sciences and between them and the traditional physical sciences. There is a continuum in science from the pursuit of the basics to application of knowledge in therapy at the bedside. The broad mission of NICHD--the study of human develoment--is a model of that continuum.

My feelings of commencement and expectation on this anniversary arise from confidence that the biological revolution will produce long-sought solutions in the years ahead; further, that this Institute, in its effort to elucidate the normal, will contribute to that achievement. We all know, of course, that the findings of basic science can neither be prescribed nor time-limited. We need time and a great deal of dedicated, difficult work. But we gain confidence from a look at the record; the past tells us that we can expect happy surprises growing out of diligent and dogged work based on the knowledge that we have painstakingly acquired.

My sense of confidence in the future of NICHD is further strengthened by the wealth of experience and knowledge brought to the directorship by Dr. Lipsett, who needs no introduction here. He brings to the post just those qualities suited to the climate of scientific development I have outlined. His work in basic science is known worldwide and his prior service as Associate Scientific Director of NICHD makes him fully familiar with the concerns of the Institute. Further, his directorship of the Clinical Center and inauguration of the new Ambulatory Care Research Facility in recent years enhance his ability to link basic research and the application of its findings to medical practice.

I want at this point to acknowledge the able leadership provided by Dr. Pickett as Acting Director of the Institute during the past year. She has served NIH and this Institute well over many years. Evidence of my respect for her abilities is the fact that I have appointed her as Director of the Division of Research Resources, a post she will assume October first. This is one of the most important components of NIH, responsible for the support of a wide range of research activities at NIH and other areas of the Public Health Service.

In the immediate future, NIH and this Institute face a special challenge--to maintain the research momentum generated in recent years and to expand the knowledge base in a period of fiscal constraints. We must strive to sustain our research capacity through stabilization of the investigator-initiated research project base. At the same time, we must continue to prepare a cadre of young scientists to carry on the research endeavor.

Through investigator-initiated research project grants, measured and tested by the peer review system, we can maintain the quality of studies we conduct and support. The same system, of competition among ideas, will assure that the most creative and promising ideas are supported, thereby assuring the high level of creativity needed to take full advantage of the knowledge base we have created.

Able leadership and a dedicated staff through the past 20 years have brought the National Institute of Child Health and Human Development to a high level of achievement. I have every confidence that this proud record will be enhanced as the Institute commences its third decade.

G. Burroughs Mider Lecture, September 15, 1982

Introductory Remarks

It is my pleasure to welcome you to the G. Burroughs Mider Lecture, part of the National Institutes of Health Lecture Series. For almost 30 years, this Series has provided a forum for outstanding scientists to present a variety of new ideas to a distinguished audience of their peers.

The Mider Lecture was established in 1968 to recognize important contributions of NIH intramural scientists to biomedical research. The lectureship was named in honor of Dr. G. Burroughs Mider who, as the first NIH Director of Laboratories and Clinics, devoted himself for eight years to developing and building the intramural research programs of NIH.

The standards of research excellence that Dr. Mider worked so hard to achieve remain with the NIH to this day. This year's recipient of the Mider Lectureship Award, Dr. William E. Paul of the National Institute of Allergy and Infectious Diseases, is an example of the high calibre of our NIH scientists. Dr. Paul is one of the leading figures in cellular immunology in the United States, and his laboratory has become one of the major training centers in modern immunology.

Born in New York, Dr. Paul was graduated summa cum laude from Brooklyn College in 1956. He received his medical degree cum laude, in 1960, from the State University of New York Downstate Medical College. He served his internship and residency at Massachusetts Memorial Hospitals in Boston. In 1962, Dr. Paul came to the NIH for a two-year appointment as a Clinical Associate in the Endocrinology Branch of the National Cancer Institute.

Leaving the NIH in 1964, Dr. Paul joined the staff of New York University School of Medicine where he began his studies of the immune system with Dr. Baruj Benacerraf. In 1968, Dr. Paul returned to the NIH to join NIAID's Laboratory of Immunology under Dr. Benacerraf. He became acting chief of the Lab in 1970, and its chief in 1971.

Dr. Paul is the recipient of numerous honors including election to the National Academy of Sciences and winner of the Texas Instruments Foundation 1979 Founders' Prize. He is also past President of the American Society for Clinical Investigation.

As Chief of the Laboratory of Immunology, Dr. Paul has successfully directed a broad research program aimed at achieving a better understanding of the activation and specificity of two classes of white blood cells--T cells (thymus-derived) and B cells (bone marrow-derived). Dr. Paul and his colleagues are among the leaders in describing and characterizing lymphokines that control the proliferation and differentiation of these cells. He is also well known for his work on the role of immune response gene products in the regulation of T cell activation.

Recently, Dr. Paul shifted his research focus to B cells, whose primary function is the production of antibodies. Although the chemistry and molecular genetics of B cell products are well known, understanding of their functional heterogeneity and activation is still limited.

Tonight, we are privileged to hear Dr. Paul discuss "Living with Lymphocytes, or B Lymphocytes and How They Grow."

Dr. Paul.

U.S.-FRANCE BIOLATERAL MEETING*

SCIENCE AND TECHNOLOGY COOPERATION

Remarks

by

James B. Wyngaarden**

I hardly need to tell this group that the biomedical sciences are advancing at an unparalled rate of change. In the course of one generation, our knowledge of basic biological processes and of technologies by which we can explore and apply these processes has expanded in an explosive manner. No generation in the course of human history has experienced such a rapid accumulation of knowledge with such profound implications for human health and potential for the amelioration of the burden of disease.

Applications of new knowledge and technologies are emerging rapidly and are already having major impacts on the practice of medicine, the prevention of disease, and the provision of health care. France and the United States, together with other countries, have been major partners in these developments. The new discoveries were not made in isolation, and we cannot hope to achieve maximum benefit from them in isolation.

Virtually every field of medical research and practice is being strongly influenced and changed by these recent advances. Progress is being achieved by a balanced relationship between the inspiration and initiative of individual

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*State Department, Washington, D. C., September 17, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

scientists and the support and encouragement of society's institutions--government, universities, industry, foundations, and other types of organizations. In the United States, these developments reflect the foresight of our society's leaders after World War II when they determined we should have a sustained, well-supported effort in biomedical research. This policy has been continued through the different administrations of government of the past 35 years and has led to the development of our National Institutes of Health and strong research groups in our academic and industrial institutions.

The array of opportunities that lie before us pose particular challenges in the governmental sector, which has a critical role in this effort. A central concern is the allocation of available resources.

- How much should be devoted to basic research and how much to its application in clinical research?

- How much should be set aside for investigator-initiated research and how much should be used for directed, targeted research? For the latter, how do we decide those targets?

- How do we establish priorities in research?

- How much should be used for the training of future researchers?

There are not enough financial resources or trained investigators to explore fully all the opportunities open to us. Budgetary constraints only sharpen the necessity to weigh alternatives and make the best possible judgments. We in the U.S. do not have clear answers to all these questions but we do have a healthy, vigorous dialogue among the concerned segments of our society--the scientific community, Congress, public interest groups, academic institutions, etc.

There are additional challenges that also result from advances in the biomedical sciences and technology:

- How do we promote the application of new technologies into the practice of medicine? Society expects that of us--especially those segments of society still underprivileged and burdened with disease. We are learning that a closer interaction between government and industry can facilitate the prompt transfer of knowledge to application.

- How can we be sure new medical technologies can be effectively and safely applied? We need to go beyond the old approach of trial and error, but our methods for technology assessment require much refinement.

- Our ability to manipulate genetic material is one of the major new features of biomedical technology. We are confident that

the potential biohazards of such technology can be properly controlled. However, the potential benefits are intermingled with ethical concerns in the use of such technology when human subjects are involved.

The issues and challenges in modern medical research are not confined to the United States, but apply equally to all technologically advanced countries. With that as background, I would like to speak more particularly about cooperation between the United States and France in the biomedical and health sciences--where we are, the challenges we face, and the opportunities that exist for working together toward common goals. Our cooperation has been intimate for many years. The principal agencies of the U. S. Department of Health and Human Services, including the National Institutes of Health, the Centers for Disease Control, the Food and Drug Administration, the Health Resources and Services Administration, and the National Center for Health Statistics, have all been involved. We are pleased to have formal cooperative programs with the National Institutes of Health and Medical Research and the National Center for Scientific Research of France, and we are pleased that there are also active networks of informal relationships of a direct scientist-to-scientist nature. At present, for example, we have 19 French scientists working in collaboration with American colleagues in the laboratories of our National Institutes of Health under our Visiting Program and another 14 as Guest Scientists, conducting research projects in a variety of biomedical fields. U. S. scientists are in France under our exchange programs with INSERM and the CNRS, and others are there through nongovernmental auspices. But this exchange is not as active as 10 or 20 years ago and need to be expanded.

In this brief time I will not dwell on past accomplishments of this partnership but rather will focus on the opportunities, challenges and issues we should face together over the next few years.

First, I look forward to nurturing the spirit of this present U.S.-France review of science and technology through future joint consultations of our leaders in the health and biomedical sciences over the coming years. For example, in my capacity as Director of the National Institutes of Health, I value the prospect of consultations with Dr. Lazar in his role as leader of INSERM. Scientific knowledge in our field is growing so rapidly that close contact is needed in order to assure that our cooperative relationships achieve maximum benefit.

A second major area of interest to both countries is the growing partnership between government and industry in the health sciences. We share a mutual philosophy that such partnerships are essential. Industry plays a key role in making available new health technologies to the physician and the patient. Research of a high scientific order is being conducted by industry. In the U.S., Federal research support is now available to scientists in industry through the same competitive review process that was formerly applied only to nonprofit institutions. This new policy should be an important stimulus for bringing emerging technologies into the marketplace. The sharing of our individual experiences in fostering such partnerships can, I am sure, lead to new insights and progress as we pursue our respective courses.

Another important area of joint interest is the opportunity for scientific exchange among health scientists of our respective countries. The scientific value of such opportunities are widely recognized. Although economic and budgetary constraints are increasingly stringent, it is incumbent upon us to see that newer generations of scientists continue to have such opportunities.

Finally, both of our countries have a history of a global concern about diseases that still plague many of the lesser developed countries. The technologies which we are both developing offer new opportunities to address those problems. I hope together we can contribute to the effective application of those technologies.

In facing the new challenges and opportunities in this time of ferment in the health sciences, I hark back to the first point I made: namely, that we need to consult frequently, to review and discuss issues, to weigh the availability of resources, and to maintain the present and seek new ways of cooperation. These discussions today and the more particular ones we are having with Dr. Lazar are important steps in that direction.

REMARKS: NICHD 20th ANNIVERSARY COMMEMORATION*

By

James B. Wyngaarden, M.D.**

Although we are meeting in the fall of the year, I sense a feeling of commencement as we observe the 20th anniversary of the National Institute of Child Health and Human Development. The past two decades have seen a remarkable outburst of discovery in biomedical research. We are, as has been noted, ready to capitalize on the findings of the "biological revolution." Scientific researchers have reached the root causes of disease and disability, the cellular and molecular level of the life processes. Now, throughout the National Institutes of Health and the biomedical research community at large, there is a sense of expectation, of the nearness of answers to age-old questions.

That sort of feeling is especially appropriate at this Institute which has the specific mission of exploring the fundamentals of human development. The more we learn about the very beginning of life, the better able we will be to maintain health and overcome the maladies of the latter years. This Instsitute has made many contributions to knowledge and to better health over the past 20 years through the study of the defects and disorders of birth and development. But, in the long run, I think the major contributions will be seen to have arisen from the meticulous study of what is normal--through the understanding of what is normal, we can eventually overcome the abnormal.

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*Presented at the 58th Meeting of the National Advisory Child Health and Human Develoment Council held on September 20, 1982, at 8:30 a.m. in Wilson Hall, Building 1, National Institutes of Health, Bethesda, Maryland 20205.

**Director, National Institutes of Heath

Because it is given a broad mission, the establishment of NICHD broke new ground in the organization of the research endeavor at NIH. The Institute's charter recognized the unity within the complexity of the life process. That was a break from the disease-specific orientation of the earlier Institutes. As we pursue biomedical research into the next century, I believe there will be increased recognition that fundamental studies are the key to the conquest of a broad array of seemingly disconnected disorders. In practice, of course, a cross-feeding of knowledge and an interdisciplinary approach is common among biomedical investigators. In fact, there is growing interchange within the biomedical sciences and between them and the traditional physical sciences. There is a continuum in science from the pursuit of the basics to application of knowledge in therapy at the bedside. The broad mission of NICHD--the study of human develoment--is a model of that continuum.

My feelings of commencement and expectation on this anniversary arise from confidence that the biological revolution will produce long-sought solutions in the years ahead; further, that this Institute, in its effort to elucidate the normal, will contribute to that achievement. We all know, of course, that the findings of basic science can neither be prescribed nor time-limited. We need time and a great deal of dedicated, difficult work. But we gain confidence from a look at the record; the past tells us that we can expect happy surprises growing out of diligent and dogged work based on the knowledge that we have painstakingly acquired.

My sense of confidence in the future of NICHD is further strengthened by the wealth of experience and knowledge brought to the directorship by Dr. Lipsett, who needs no introduction here. He brings to the post just those qualities suited to the climate of scientific development I have outlined. His work in basic science is known worldwide and his prior service as Associate Scientific Director of NICHD makes him fully familiar with the concerns of the Institute. Further, his directorship of the Clinical Center and inauguration of the new Ambulatory Care Research Facility in recent years enhance his ability to link basic research and the application of its findings to medical practice.

I want at this point to acknowledge the able leadership provided by Dr. Pickett as Acting Director of the Institute during the past year. She has served NIH and this Institute well over many years. Evidence of my respect for her abilities is the fact that I have appointed her as Director of the Division of Research Resources, a post she will assume October first. This is one of the most important components of NIH, responsible for the support of a wide range of research activities at NIH and other areas of the Public Health Service.

In the immediate future, NIH and this Institute face a special challenge--to maintain the research momentum generated in recent years and to expand the knowledge base in a period of fiscal constraints. We must strive to sustain our research capacity through stabilization of the investigator-initiated research project base. At the same time, we must continue to prepare a cadre of young scientists to carry on the research endeavor.

Through investigator-initiated research project grants, measured and tested by the peer review system, we can maintain the quality of studies we conduct and support. The same system, of competition among ideas, will assure that the most creative and promising ideas are supported, thereby assuring the high level of creativity needed to take full advantage of the knowledge base we have created.

Able leadership and a dedicated staff through the past 20 years have brought the National Institute of Child Health and Human Development to a high level of achievement. I have every confidence that this proud record will be enhanced as the Institute commences its third decade.

THE FUTURE ROLE OF BIOMEDICAL RESEARCH IN THE ACADEMIC HEALTH CENTER*

by

James B. Wyngaarden, M.D.**

I suspect that most of you have read the article that appeared in JAMA last February on "The Four Horsemen of the Apocalypse" by Bob Petersdorf and Marjorie Wilson[1]--and that you know the paper was neither a Bible commentary nor a nostalgic piece on football.

The authors used the well-known allegory of the Four Horsesmen from the Book of Revelation to characterize the officials who commonly run academic medical centers--the Vice President, the Dean, the Department Chairman, and the hospital Administrator.

In the Biblical account, the apocalyptic rider on the black horse held a pair of balances signifying famine. This rider could be none other than a symbol of the Vice President for Health Sciences. He has a more than passing acquaintance with financial austerity, if not with famine. It would be a strain on scriptural authority, however, to accept the interpretation made by some that one pan of the balance carried by the rider of the black horse symbolizes "direct costs" and the other "indirect costs."

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*Presented at meeting of Association of Academic Health Centers, Kiawah Island, South Carolina, on September 29, 1982.

**Director, National Institutes of Health.

[1]JAMA, February 26, 1982, Vol. 247, No. 8.

Nevertheless, the symbolism of the scales is apt because there is no question about the Vice President's responsibility for balancing many forces and interests, including the budget. Another feature of the analogy not mentioned in either JAMA or the Scriptures is the likelihood that the rider of the black horse was saddle sore. The Vice President rides a fractious mount, whose moods are unpredictable.

My predecessor, Jim Shannon, once characterized the academic medical center as " . . . an organizational disaster--cumbersome, administratively chaotic, and unstable to a high degree . . . and its basic instability, not yet manifest in its younger programs, will have mounting significance . . ." "In fact," he concluded, "one might compare the typical university medical center to a hotel in which each guest can build a wing of his own and demand service."[2]

Dr. Shannon made his comments on the academic medical center just before he retired as NIH Director--and since I have no such plan, I'll not comment on or embellish his pungent remarks other than to say that I have some understanding and appreciation of the difficulty of your job. I recognize that the support of research is only one of the variables in the unruly financial equation that you are required continuously to keep in balance. But even though it is one element among many, research is not a minor component of institutional responsibility or of your fiscal concerns.

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[2]Transactions of the Association of American Physicians, Vol. lxxxi, 1968.

Academic health centers and the National Institutes of Health represent new concepts of organization--neither of which has much more than two generations of history. I am confident, however, that any fair evaluation would find that each has served well its important purposes and that our partnership has been highly productive.

I welcome this opportunity to meet with you because you represent the largest group, by far, of the NIH's institutional partners in biomedical research. For me, the occasion is particularly timely since I have begun seriously to engage a constellation of issues that will affect the Federal-academic relationship in the years ahead.

Almost every topic that has appeared recently on the agenda of senior staff meetings at the NIH would be highly appropriate for discussion here--permit me to name a few: stabilization; center grants; misconduct; small business set-asides; new institutes; grant support for salaries of tenured faculty; replacement of obsolescent equipment; sliding scale grants; the extramural budget versus the intramural; and last but not the quietest, curtailment of the indirect cost allowance.

A common thread through most of these issues is budget, and there is no escape from the conclusion that our decisions regarding them will be heavily influenced if not determined by the fiscal actions of the Administration and the Congress. But I believe we must seriously consider such topics in the round and not just see them as silhouettes against the rather cloudy horizon of Federal funding for the '80s.

Public confidence that scientific research is an appropriate and necessary government activity was immeasurably strengthened by the experience of World War II. It was also in the war years that the partnership of the Federal government and academic medical institutions was found to be effective, practical, and highly useful. Since that time, there has been no significant change in the basic principles shaping the partnership. During most of the history of the NIH, certainly for the past 10 to 15 years, about four-fifths of the Agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. A large portion of that support goes to academic health centers for the compelling reason that you have a national resource for which there is no substitute--your faculties of trained basic and clinical scientists. And further--one of your central purposes is to insure the continuing renewal of that precious resource--the trained investigator.

While budgets--the availability of necessary funding--is a common thread running through our concerns for the future, there is another consideration equally as important; that is the absolute necessity for assuring that an adequate number of the finest and the brightest young minds in the current and coming generations find careers in biomedical research. No amount of coercion could accomplish the goal. An adequate number of first-class biomedical research scientists for the 1980s and the 1990s can only be maintained if graduate schools and academic health centers are successful in nurturing research career interests of the young people who come to them for training. It is just as important that during their years in training such young people have a reasonable expectation that once their formal training is completed, they will

have opportunities to apply themselves to research studies in their fields of interest.

It is hardly revolutionary to suggest that ample funds for the support of project research is an incentive for young scientists to choose research as a career and to stay with it.

But when the funding available for project grants levels off--and, at the same time, the size of the average grant is growing--something has to give. The most vulnerable segment of our research support portfolio--new and competing grants--absorbs the shock. To avoid further closing the portal to the NIH project grant programs, we have appealed to the Administration and the Congress to help us maintain a relatively stable number of new and competing grants from year to year. Generally speaking, their response to our stabilization effort has been favorable and supportive, as far as possible, of our premise that 5000 new and competing grants each year are needed to maintain stability.

We hope that the stabilization effort will send a clear signal to the young investigator that even in a time of constrained budgets, research support from the NIH is not restricted to the very few.

As you know, NIH has relied on the investigator-initiated project grant as its prime mechanism for the support of biomedical research. During the fiscal year that ends tomorrow, the NIH budget supported almost 16,000 project grants.

Almost exactly 50 percent of our $3.6 billion budget for 1982 was used to fund such project grants.

The point of stabilization, of course, is to assure that a predictable and substantial number of new or competitive grants can be made each year. Under normal circumstances, between one-third or one-fourth of the grants we award each year are in the new or competing category. The stabilization strategy is based in part on our experience that over half of our new project grants each year are made to first-time principal investigators. Responsibility for the future productivity of the research enterprise rests heavily on these newcomers and it is not only prudent, but it is also essential, that this door be kept open. Another facet of the stabilization effort is in response to the need to maintain research training programs at predictable levels. The NIH supports only a fraction of the scientists in research training, but it is an essential fraction necessary to the replenishment of the critical mass of first-class scientists.

While we regard the purposes of stabilization as imperatives for the 1980s, we, at the same time, are aware that our efforts to maintain the highest possible level of project research support in the face of a constrained total budget can bring on undesirable side effects complicating and possibly clouding our relationships with grantee institutions. Our attempts to maintain opportunity for new investigators also can affect our ability to support

established investigators who, in mid stream of their most productive years, have need for increased rather than diminished funding.

So the rider on the black horse of the apocalypse is not alone in using balance scales.

The 1983 budget for the NIH is the resultant of a variety of fiscal forces. A central concern was the need to assure that funds for new and competing grants would not be severely reduced.

As finally agreed upon, the proposed budget would permit the awarding of 4100 new and competing grants, a reduction of some 641 from the number to be awarded in 1982. It was our feeling that at least 4100 such grants represent a critical minimum if we are to maintain momentum in bringing new investigators into the project grant system. In order to meet this minimum requirement, it was necessary to continue the three to four percent reductions that had been negotiated in continuing grants last fall, and to project funding for indirect costs at 90 percent of the previously determined rates for all research grants.

It is not our intent that this 10 percent reduction be a permanent measure, nor do we have any doubt about the fact that indirect costs are real. We are concerned that indirect costs are rising faster than direct costs and that over a fifteen-year period, the overhead has risen from about 15 percent of the total cost of the average award to the present 29.5 percent. The basic issue is the extent of cost sharing by grantee institutions.

So in the context of the 1983 NIH budget, the reduction of indirect costs and the reduction of three to four percent in direct costs of continuing grants represent a distribution of budgetary restraints across both components of the project grant budget.

The proposal to limit the indirect cost allowance engendered concerted and vigorous opposition from administrators of grantee institutions, who see it as an arbitrary and unilateral abrogation of financial commitments and established principles. At the same time, the proposal has been greeted generally with applause from grant-supported scientists. The reduction of direct cost allowances has not generated a comparable decibel level of complaint from either investigators or institutions.

Some publicity has been given to a proposal that the NIH support for project research could be spread over a larger number of investigators by the adoption of a sort of sliding scale. This approach would mean that the amount of direct costs as estimated by the principal investigator and considered by our reviewers to be necessary would be awarded only to the grantees whose applications receive the highest priority scores. All other awards would be made at progressively lower levels depending on the priority score.

While this approach has attractive features and would spread the funding among a greater number, it does not take into account the fact that there is a critical quantum of support below which many of our projects would become ineffective. A mechanical application of a sliding scale principle would negate

the considered judgments of study sections as to the essential components of proposed projects.

This is not to say that we believe the present system is perfect and would not benefit from change. I do feel, however, that we should consider most carefully any modification of the process of review and award that has served so well for three decades. We need and would welcome any suggestions you or your colleagues might offer as to ways and means for dealing with the complex of issues centered on the vital project grant programs of the NIH.

I have been questioned in various forums about the fact that the proposed NIH budget for 1983 includes an increase of seven percent for intramural programs at a time when the increase requested for the overall budget is three percent. I think it would be useful to put that issue in perspective.

It should be remembered in discussing this issue that the intramural budget represents just over one-eighth or 13 percent of the total NIH appropriation.

In developing the FY 1983 budget, we faced the kind and degree of issues with which you are all too familiar in academic medical centers. Most of the additional funding for intramural programs will be used to cover mandatory cost increases such as utilities, the Congressionally authorized FY 1982 pay raises, and the higher costs of supplies and equipment. Our personnel costs make up about the same major proportion of our budgets as yours do and, like you, we have a tenure system, which if anything is more extensive than in academic

institutions. But unlike the academic budget, we have a single source of funding--our Congressional appropriation.

In addition, a substantial part of our intramural increase this year--about a sixth of it--was to provide funds for initial stages of the operation of the large Ambulatory Care Research Facility whose construction has just been completed. An alternative would have been to seriously retard the schedule for activation of the $100 million facility.

Since 1977 the intramural research budget has grown by 11.2 percent in constant dollars. During the same period, our emphasis on stabilization has been responsible for a real increase for project grants of 16 percent. This increase in project grants has been made at the expense of R&D contracts which decreased by 46 percent, and of center grants by 25 percent. Consequently, the extramural budget as a whole has lagged five percent behind inflation, but during the same period, the total NIH budget has lagged by 8.5 percent.

I am certain that you will be interested in the topic which will be the principal item on the NIH Director's Advisory Committee's agenda when it meets late in October. We plan to discuss the implications of and possible alternatives to our present practice of including some or all of the pay of the investigator as direct project expense.

At a time when the NIH budget was on a steeply ascending curve, in the mid sixties the Wooldridge Committee report identified the practice of charging faculty salaries directly to grants as "clearly divisive in effect," and commented, "The investigator's own pay is, to him, different in kind from any other item of expense in the total budget of his project. It has emotional significance: it is a symbol of his 'belonging,' in some sense, to whatever organization provides the pay."[3] The Wooldridge predictions of divided loyalty have been realized and the adversarial relationship between research faculty and institutional administration is a subject that I need not attempt to elucidate to this audience. Equally as serious is the fiscal fallout of the practice.

Twenty-five years ago, it was considered inappropriate to ask for investigator reimbursement on research grants. The contention was based on the principle that a faculty member was appointed to do research, teach, and provide public service. As the research enterprise grew and administrators recognized the advantages of freeing institutional funds to acquire more faculty, the practice of requesting salary for time spent on a given project increased. In some institutions the faculty balked at the idea, concerned that the inclusion of faculty salaries in a grant application might be viewed unfavorably by Study Sections and lessen the chances of approval. Very slowly, initial review groups came to accept the inclusion of investigator salaries. The institutions justified the practice on the ground that the salary reimbursements would make

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[3]Biomedical Science and It's Administration: A Report to the President, February 1965, p. 29.

available the institutional funds needed for hiring other persons to pick up teaching loads so that the investigators would be free to spend more time in the laboratory. Inclusion of salary on grants was originally designed to provide release time and, in the institutions where nine-month appointments prevailed, to provide summer salaries for investigators.

The amount of salary requested came to be equated with the total time spent on a research project and not merely the increment over the university's commitment for support of research. The practice continued until the faculty members' spontaneous cooperation in bring in funds to help their institution become an implied obligation to generate income. A somewhat similar obligation in the case of clinical research faculty has since been transferred to providing income from patient care.

But instead of hiring young instructors on a part-time or replacement basis, the funds recaptured from salary reimbursement often were pooled at departmental or institutional level and used to employ full-time faculty, most of them tenured. This has led to overcommitment in tenured positions by many institutions or, at the best, has made the recoupment of research salary funds a vital necessity.

No figures are available on the amount of money NIH now pays in tenured faculty salaries, but there can be no question about the very large extent to which grant funds are woven into the fabric of institutional funds.

The magnitude of the sums involved and the nature of the relationships between and among NIH, the institutions, and the investigators are such that if any change is decided upon, it should be developed in negotiations among all parties and phased in over a period of time.

It would be premature for me to advance any particular solution or to discuss in depth the possible alternatives. I will mention a few of the suggestions that will be presented to the Director's Advisory Committee:

One approach would be for the NIH to pay investigator salaries on the basis of documented man-months of released time rather than on the basis of percentage of effort--a pattern set by the NSF. Another would be to place an arbitrary cap on the amount to be paid in salary reimbursement.

An alternative suggested by the Wooldridge Committee to avoid the divisiveness of "outside support" is worth considering in the broader examination of the salary issue--the Committee said, "If NIH wants to reinforce the ties between the investigator and his institution, there can hardly be a better method than by ensuring that any contribution from NIH to the investigator's own pay is made thoroughly by the way of the institution, and that he is not reminded of this contribution either when he makes an application or at any other time."[4]

The mechanism for carrying out this suggestion would be an institutional faculty research salary grant.

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[4]Biomedical Science and It's Administration: A Report to the President, February 1965, p. 29.

From the alternatives I have mentioned, it is evident that there is much to be discussed and thought about.

It is my hope that the forum provided by the Director's Advisory Committee in open consideration of all aspects of the salary reimbursement issue will help all parties concerned to reach practical and beneficial conclusions--minimizing polarization within institutions and further strengthening the partnership between grantee institutions and the NIH in our common commitment to biomedical research and training.

I am aware that I have touched on only a few of the many matters of our mutual concern--all of which deserve full and frank discussion. Again, permit me to say how appreciative I am of this timely opportunity to meet with you. It is vitally important to the progress, even the continuation of the supremely important enterprise in which we are joined, that we understand each other as fully as possible.

FOR RELEASE UPON DELIVERY

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.
DIRECTOR
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT
AND THE
SUBCOMMITTEE ON
SCIENCE, RESEARCH AND TECHNOLOGY
OF THE
COMMITTEE ON SCIENCE AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

September 30, 1982

Chairmen Gore and Walgren and Members of the Subcommittees:

I appreciate this opportunity to discuss the setting of priorities in science. As Director of the National Institutes of Health, I will focus today on one aspect of this important topic, namely, priorities in biomedical research.

To be most responsive to the concerns of the Subcommittees, I will discuss three major areas of influence on priority setting at NIH: the overall mission of NIH, scientific considerations, and other factors of influence, such as specific public mandates and assignments as expressed by Congress and the Administration. The three areas interweave, but for purposes of discussion, I have separated them. Finally, I will briefly describe for you the research opportunities now before us.

Mission of NIH

The mission of NIH is a broad one, but it can be stated simply: "to uncover new knowledge that will lead to better health for everyone." That public commitment to biomedical research has been restated in various forms since 1887 when the Hygienic Laboratory was established at the Marine Hospital on Staten Island "for research on cholera and other infectious diseases." The mission was reaffirmed in 1930 when Congress passed the Ransdell Act, which established a National Institute of Health. At that time, the Act's author,

Senator Joseph E. Ransdell, saw a broad scope for the new Agency, telling the Senate:

> "This institution should be an international clearinghouse for health. . . . A vast amount of research work is awaiting the attention of scientists in the field of medicine and its application for the alleviation of suffering. . . . Progress in the future may be expected to depend on the advancement of scientists, and that country will be most benefited whose citizens are encouraged to engage in systematic research and aided in doing so."

Congress underscored its faith in the value of health research in 1944 when it consolidated and revised laws relating to the Public Health Service. In Section 301 of the PHS Act it gave a broad charter for the conduct of biomedical research by directing the Surgeon General to:

> ". . . conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man. . . ."

The broad intention of Congress in Section 301 was emphasized in a House report on that PHS Act, stating:

> "Part A of this title would consolidate and restate the basic authority of the Public Health Service in the whole field of research, so as to grant, in clear and unmistakable terms, broad authority to carry on investigations through its own personnel, and to cooperate and assist in the investigation by others, of all problems bearing on the physical and mental health of our people."

This expression of confidence in the potential of health research, together with a multi-billion-dollar investment, built a biomedical research capacity second to none. It is a source of National pride and international prestige. I should point out here that, while the Federal role is central and

essential, there is no Federal monopoly on health research. In speaking of the Nation's research capacity, we include laboratories in publicly supported and private colleges and universities, voluntary organizations and foundations, and the laboratories of business and industry.

NIH operates a large program of laboratory and clinical research in its own facilities, but four-fifths of the expenditures of the agency go to the support of biomedical research conducted in universities, private laboratories, and elsewhere. The Federal Government contributed nearly 60 percent of support from all sources for health-related research and development in 1981; the NIH budget accounts for about 70 percent of the total Federal investment. From the beginning, the main NIH mechanism of research support has been individual project grants for studies proposed by non-government scientists. About half of the NIH budget currently supports such investigator-initiated projects.

NIH programs express the national policy shaped by Congress through the years. That policy encourages diversity and excellence in health research; it relies on the scientific community itself to identify, through a competitive peer review process, the ideas and investigators most worthy of support. In this way, public funds invested in biomedical research support the most creative ideas and energies in the American health research community--a wealth of ideas whose range far exceeds those that could be generated by any single committee, board, council, or laboratory.

We also engage in a variety of research-related activities, such as clinical

trials to test new medical technologies and drugs and devices, community education and demonstrations, and development of orphan drugs. But they all build upon new knowledge generated through fundamental biomedical research. Our mission does not include programs of health services or delivery nor of regulation, but of course, we collaborate with agencies and organizations with such responsibilities, particularly in regard to future research needs from service and regulatory perspectives.

Scientific Considerations in Priority Setting

It is useful to think of research as a continuum stretching from investigations into the most fundamental mysteries of nature to programs designed to translate and then transfer new knowledge to the practicing physician.

The ultimate goal of biomedical research is the elimination of disease and disability: the prevention of maladies before they strike or cause damage. To prevent disease, we need to know the process--how the disease acts, and its target in the body. Sometimes we are fortunate, as in the case of polio vaccine, where a confluence of factors plus a determined public health effort removed almost overnight a cloud that had hung over society for many years. That kind of conquest of disease, however, is rare. Most often we slowly amass evidence and carefully look to place each new piece of information in a giant puzzle, in the process creating new opportunities that lead us in previously unforeseen directions.

The fundamental approach to discovery at NIH continues to be through support of investigator-initiated basic research into the life processes. Biomedical science is increasingly probing the cellular and molecular levels of function. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. Proposals are further evaluated by advisory councils for program relevance. We believe this approach will produce the ultimate answers, a belief based on the record of the past. In order to maintain the momentum of discovery, we consider it extremely important to continue to place a high priority on the award of new and competing research project grants.

Fundamental to decision-making on research priorities is the availability of a critical mass of basic knowledge with which to launch further inquiries. This point is well illustrated by a brief review of events leading to the newly licensed vaccine to combat hepatitis B virus, the cause of a debilitating liver disease.

Dr. Baruch S. Blumberg, a scientist studying human genetics with support from NIH, had been pursuing such basic studies for about 13 years when, in 1963, a substance in the blood of an Australian aborigine caught his attention. For a time he thought he had discovered an evolutionary marker in the blood of a primitive people. Some years later, he recognized that this marker was a protein fragment left by a previous infection with hepatitis B. This leap of insight opened up many new studies on the structure of the virus and,

eventually, led to the development of the vaccine. This much-foreshortened account makes several points concerning the critical importance of basic research.

First, one cannot predict where a basic discovery will have its greatest impact. In this case, an immunologist contributed to infectious disease control.

Second, there may be a long time lag between the initial research and its clinical application; in this case almost 20 years.

Third, one cannot direct an application before the basic knowledge is available. Had planners decided in the mid-1950s to develop a vaccine against hepatitis B, no one would have known where to begin. As Dr. Blumberg said in his address in accepting the Nobel Prize in 1976: "At the outset we had no set views on where this path might lead. . . . I could not have planned the investigation at its beginning to find the cause of hepatitis B." Where this work will lead in the future is an open question, but it has important implications--recent research on the hepatitis B virus has suggested an association with liver cancer, the most common form of cancer on a worldwide basis.

A corollary to the investigator-initiated approach is the need to assure a continuing supply of well-trained scientists to carry out the research needed to meet national health goals. There is a close and reciprocal relationship between the continued productivity of research and the availability and

replenishment of the supply of qualified investigators. There also exists a special need to replenish the supply of physician investigators and, accordingly, we are making every effort to attract a sufficient number of investigators capable of conducting clinical research.

All research planning, then, proceeds from what is known about a health problem, life process, or disease area. Such a review leads to the identification of scientific opportunity, gaps and needs, and rapidly advancing areas of research. We also review potential interventions ready for clinical testing and approaches or emphases required to advance the knowledge base further. Closely allied is a consideration of the existence of adequate research resources. Modern biomedical research demands sophisticated equipment and instrumentation to maintain high quality of work. The aim is to move along the continuum from basic research to treatment at the bedside.

The selection of priority areas for clinical research depends on assessments of:

--The physical, emotional, societal, and economic costs of various diseases.

--The readiness of the state of knowledge for application to disease prevention or treatment.

--The potential impact of various research strategies on reducing the burdens of disease.

I would like to cite here three examples that, in varying ways, reflect these assessments.

One example is the National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute, which is based on the knowledge that hypertension is a major factor in stroke and heart disease. In this program, public education on factors that contribute to hypertension is conducted through cooperation with a wide range of public and private organizations and institutions and with business and industry. This program, and the findings of biomedical research, have contributed to a greater public awareness of the importance of nutrition, exercise, non-smoking and other personal practices in the reduction or prevention of high blood pressure.

Other diseases may receive high priority because they provide unique research opportunities despite their relatively low prevalence or limited geographic distribution. These comparatively rare diseases may have well-defined metabolic or genetic characteristics that make it possible to study underlying mechanisms that also occur in more prevalent diseases but are masked by complicating changes.

An interesting example is Huntington's disease, which is a genetic disorder of low prevalence in the United States. However, the National Institute of Neurological and Communicative Disorders and Stroke has given priority to a study of this disorder in collaboration with scientists at a university in

Maracaibo, Venezuela. A population of 200 patients descended from a Spanish sailor who arrived in the country in 1860 is providing a unique opportunity to study an inherited disease with neurologic manifestations that are similar to those in Parkinson's disease. This is a valuable approach because the neurologic manifestations of the more prevalent Parkinson's are less well defined than those in Huntington's disease.

Finally, pursuit of fundamental answers in biomedicine not only leads to new ways to alleviate or control disease and disability, but also to cutting the costs of health care. An example is the practice of treating kidney disease by kidney dialysis and transplantation, great achievements of biomedical research that have restored and prolonged many lives. But this approach is costly and can only compensate for the damage already caused by disease processes we do not fully understand. Therapy of this kind has been termed "halfway technology" by Dr. Lewis Thomas. Consequently, one of the highest priorities of the National Institute of Arthrities, Diabetes, and Digestive and Kidney Diseases is to support research into the major diseases that lead to irreversible renal failure so that we can prevent or arrest them.

The Nation's approach to investment in research has paid off in lives saved, in disabilities overcome, and in economic benefits. One economic analysis of the period 1900 to 1975, for example, estimated savings from reduced morbidity and mortality at between $300 and $480 billion. Taking the conservative estimate, this indicates a return of at least $10 for every dollar invested in health research. (Mushkin, S.J., 1979, "Biomedical Research: Costs and Benefits," Cambridge, Mass., Ballinger, p. 412.)

Other Considerations in Priority Setting

In setting research priorities, we also give major consideration to the concerns and wishes of the public, expressed directly and through Congressional and Executive Branch actions. Authorizing legislation, mandates, directives, and appropriations all influence our research planning and the conduct of our programs. A few examples of Congressional actions that set our course are: concern for providing greater support to specific areas of research or studies; mandates to allocate a proportion of resources to a particular disease area; directions for long-range plans; changes in research training legislation; proposals for small business set-asides; and the establishment of new Institutes with specific charges.

Additionally, an important part of the planning process involves the views of professional societies and voluntary health organizations, the biomedical research community, and the general public. These views are sought through a variety of means, ranging from structured activities such as National Advisory Councils, special groups or task forces or commissions to consider specific research areas or health problems, to less structured interaction with representatives of such groups as conditions warrant.

Within NIH there are comprehensive and highly organized processes for setting priorities within each Bureau, Institute and Division. The priorities are eventually integrated within the Director's office as part of the annual budget process.

Research Opportunities in the 1980's

Three decades of vigorous public support of biomedical research have now produced a knowledge base that offers unparalleled opportunity for capitalization by the public and private sectors of the research community. Let me cite some examples:

The development of recombinant DNA technology gives us an exciting tool with which to transfer hereditary units from one species to another. It permits, for example, bacteria to become "factories" that produce substances of biological, agricultural, and medical importance. This technique has already led to the synthetic production of human insulin, somatostatin, and growth hormone. These substances are now being tested in NIH-sponsored clinical trials to determine their effectiveness in treating insulin-dependent diabetes and certain types of dwarfism. Recombinant DNA technology can also yield large quantities of pure antigen which, in turn, may soon be used in vaccines for immunization against infectious agents.

In addition, large quantities of highly specific antibodies can now be produced in the laboratory from hybridomas produced by cell fusion. This process results in monoclonal antibodies that can be used with great precision in research on vaccines, diagnostic tests, and treatments for many diseases. Recently, for example, investigators used human lung cancer cells to prepare monoclonal antibodies that can distinguish human tumor cells from normal cells. This technology might permit the detection of cancer at a very early

stage. Eventually, clinicians may be able to attach radioactive or chemotherapeutic agents to the antibodies and thereby kill cancer cells without harming surrounding tissue.

Remarkable progress has been made in understanding the immune system. Scientists have discovered genetic mechanisms that control the immune response to such invaders as cancer cells, transplanted organs, and environmental substances that cause allergies. The genes that regulate these immune responses are called the major histocompatibility complex (MHC). Further knowledge of MHC in relation to many diseases--juvenile-onset diabetes, certain kinds of arthritis, Alzheimer's disease, chronic hepatitis, myasthenia gravis, and others--may lead to better strategies for resisting them and to better techniques for organ and tissue transplantation.

An especially fruitful and expanding area is research in neurobiology. Investigators are finding many substances that have profound effects on the nervous system--endogenous neurotransmitters and neurohormones, as well as many externally applied pharmacologic agents. Such substances act at "receptor sites" in many locations within brain and nerve tissue. Some recently discovered examples are the body's natural painkillers--the endorphins and other opiate-like substances--which may provide fuller understanding of the mechanisms of brain function, the cause of substance abuse or drug addiction, and the treatment of pain. Their discovery has opened a whole new arena of research which may well lead to the conquest of illnesses of the mind and mood, such as depression, that have long baffled medical science.

Two new research instruments--the PETT Scanner (Positron Emission Transaxial Tomography) and the NMR Scanner (Nuclear Magnetic Resonance)--are generally regarded as promising and versatile technologies that provide noninvasive methods for the study of organ structure, function, and metabolism in living subjects. Like the CAT Scanner (Computer-Assisted Tomography), they promise to have a major impact on diagnostic medicine in the future.

These scientific advances form the base upon which we will build important achievements and health benefits in the years ahead. They will not come quickly or easily, but there is a momentum to science that gives me confidence in the future. We are closing in, I believe, but we still must understand the fundamental processes and mechanisms of heart disease, cancer, stroke, schizophrenia, arthritis, diabetes, and other major diseases. We must set our priorities in full awareness of the enormous toll of such disorders, their complexity, and the state of knowledge and readiness for discovery that I have outlined.

Conclusion

We recognize and strongly believe that specific research priorities should be set most carefully. We would do the progress of science a disservice if we, as managers, were to become preoccupied with short-term objectives. The power of science is generated by the creative genius of the individual scientist or research group. We can best encourage creativity and assure quality by providing adequate resources and prudent guidance.

Thank you for the opportunity to present these views on research priority-setting in biomedical science. I will be pleased to answer any questions you may have.

-fpw-9/28/82

NEW DIRECTIONS: A TALK WITH THE NIH DIRECTOR

STEP Forum Series
September 30, 1982
2:00 - 4:00 p.m.
Building 1, Wilson Hall

Contact: Steven J. Hausman
496-7495

Please return to:
Dr. James B. Wyngaarden
Room 137, Building 1
NIH
Bethesda, MD 20205

I. Amenities

II. Introduction

A. I welcome this opportunity to meet with you and explore some areas of particular interest to the extramural staff.

B. I have heard only good things about the STEP program, now entering its second decade [1972-1982].

C. Since you are serving and training as operators and emissaries of NIH's extensive award programs, it is important that we understand each other well on matters of NIH policy.

D. I hope we have many opportunities to meet, both individually and together.

III. New Directions

A. Our theme today is "new directions." I sometimes reflect on the new challenges that faced each NIH Director:

- Dr. Sebrell considered the opening of the Clinical Center his major responsibility.

- Dr. Shannon was concerned with spending wisely a rapidly expanding budget--from $80 million in 1955 to about $1 billion in 1968. NIH in those years not only supported excellent research but also helped to build the Nation's research plant.

- Dr. Marston's challenge was to develop the Nation's health manpower, a program that rose from about $160 million in 1969 to $595 million in 1973, when it was transferred to HRA.

- Dr. Stone had to deal with the politicizing of NIH and the impoundment of some $230 million dollars in his first year.

- Dr. Fredrickson, as I see it, faced three major challenges:

  --To define and set the boundaries of the NIH mission (medical research and applications but not health care delivery),

  --To establish a system for going forward with recombinant DNA research with adequate safeguards (but not Federal regulations),

  --To stabilize NIH research grant and training programs.

- My own challenge, it appears, will be to guide NIH in the face of depleting budgets--to make the most of what we have. I don't want to leave the impression, though, that budget tribulations are of recent origin. Over the past decade, NIH has been funded by 6 appropriations and 24 continuing resolutions.

B. NIH is indeed moving in new directions as dictated by two pervasive trends:

- A shrinking research dollar (a stable dollar shrinking in purchasing power) and

- Our mounting efforts to maintain the creativity and excellence of NIH programs.

C. These trends have a number of implications for program direction. They will largely dictate policy in the foreseeable future.

SLIDE 1 5

IV. Shrinking Research Dollars

A. In 1979 the aggregate NIH appropriation was $3.2 billion.

B. Although this has increased to $3.6 for fiscal 1982, the trend is definitely downward in purchasing power.* 1979 was our peak year in constant [1972] dollars. [Slide should read $3,642 with supplement for OD, NLM.]

C. Dwindling resources compel us to focus more sharply on research priorities, program balance, and the degree to which we target our research efforts.

D. Let's take a look at some significant trends in NIH programs:

*Determined by the biomedical R&D price index. Consult OPPE's Division of Program Analysis, Program Analysis Branch, 496-9291.

SLIDE 2 6

E. The fiscal history of the Institutes in constant dollars gives us insights into program balance.

- The gentle rise of the aggregate is seen here to be a nearly steady state for most of the programs, with NCI as the major exception.
- Dental Research and General Medical Sciences have dropped off a little.
- DRR is treated as though it has always had the General Research Support (formula grant) appropriation, and is trending downward.
- NLM, not shown here, is a flat line, dropping in 1981.
- The point is that each BID is a separate entity. It's fate must not be obscured by the aggregate as we think in terms of total appropriations or award mechanisms.

SLIDE 3 7

V. Trends in NIH Awards*

A. Still, it is instructive to view the extramural programs en masse. Research grant awards increased from $700 million in 1971 to $2.3 billion in 1981--more than tripled.

B. R&D contracts, over the same period, rose about 150 percent. Actually, they reached a peak of $465 million in 1979, then dropped more than $100 million in the last two years.

C. Training awards ranged from a low of $120 million in 1976 (discounting the fluctuation due to the impoundment and release of funds in 1973-74) to $180 million in 1980.

D. In a moment we'll review these program areas in terms of constant dollars.

*Excludes NLM. Thus differs slightly from DRG's Extramural Trends.

SLIDE 4 8

VI. Grants vs. Contracts

A. The relative magnitude of the research grant and R&D contract funds is revealing.

B. Since 1974, the grants have been steadily increasing as a proportion of all awarded funds, rising from 67 percent in 1974 to 81 percent in 1981.

C. Conversely, the contracts have decreased from a peak of 23 percent in 1975 to 13 percent in '81. For the past three years, the decline has been steeper--2 to 3 percentage points a year.

D. The effort to sustain the level of new investigator-initiated awards--that is, research project grants--has strongly contributed to these trends in the past two years.

SLIDE 5 9

VII. Average Size of Research Grants

A. One way to explore the dynamics of these trends is to examine the average size of various types of award.

B. Between 1971 and '81, the average research project grant (R01, P01, and other) increased from $51,500 to $107,000

C. But if we adjust for inflation, we are back to $51,000. In other words, the average grant bought about the same amount of research in 1981 as it did a decade earlier.

SLIDE 6 10

D. Some would argue that the rising proportion going to indirect costs--from about 21 percent to 29 percent--deflated the research dollar still further.

Indirect costs are vexing issue of the year. For 1983, indirect costs to be reduced 10 percent from negotiated amounts. We are looking at the problem for '84.

SLIDE 7 11

E. If the average grant has remained at the same level in buying power, then the steady increase in numbers of awards shows real growth in these programs. NIH awarded about 10,000 project grants in 1971 and 17,000 in 1981.

SLIDE 8 12

VIII. Trends in RO1s and PO1s

A. Let's return to cost trends for research project grants and glance at the two major kinds--traditional (RO1s) and program projects (PO1s).

SLIDE 9 13

B. This slide isolates the two trends. RO1s rose from about $370 million to $670 million in 1971 dollars. In other words, the program has nearly doubled in real terms.

C. The PO1s rose from about $106 million to $156 million in 1980, a real increase of nearly 50 percent.

D. Meanwhile, the award rates for research project grants are dropping. In 1971 we were able to pay 51 percent of the number eligible; in 1981, only 39 percent. Unfortunately, many sound proposals are going unfunded.

E. But this assures us, of course, that the quality of our investigator-initiated awards is not dropping as the volume increases.

SLIDE 9 (CONT.) 14

F. And these high-priority programs are thriving in the face of chronic budget constraints.

Our present policy is to continue funding the most meritorious research. Have looked at various egalitarian proposals, such as "sliding-scale" grants. But the fact remains that the best is vastly better than the next best. How to get more out of the grant dollar, however, is by no means a closed issue.

SLIDE 10 15

IX. The Average Research Center

A. Research centers present a similar picture.

B. Over the decade, the average center grant has cost about the same in constant dollars.

C. There has been a decline in funds going to centers in relation to other kinds of research grants--from about 22 percent in 1973 to 16 percent in 1981.

D. But the number of centers rose from 402 to 520--again representing strong program growth.

SLIDE 11 16

X. The Average R&D Contract

A. As I have indicated, the trend in R&D contracts does not parallel the trend in grants.

B. In 1971 dollars (dotted line), the average contract went from $122,600 to about $133,000.

C. Nonetheless, the current trend here appears to be downward. The 1979 peak was about $145,000. So the real change is a decline from that point of about 8 percent in the average award.*

*The 1974 peak is ignored, as it was due to release of impounded funds.

SLIDE 12 17

D. Meanwhile the number of contracts dropped from about 2,200 in 1977 to 1,300 in 1981.

SLIDE 13 18

E. There has been a decline in the proportion going to institutions of higher education, from 44 percent of contract dollars in 1972--probably an all-time high--to 31 percent in 1981.

F. Medical schools got about 30 percent of R&D contracts throughout the '70s, but dropped to 24 percent last year.

19

XI. New Directions

A. I believe we can conclude from all this that NIH has responded to the 1970s plateau and downturn in purchasing power by modifying the way it does business. We are returning to more traditional ways of funding research.

B. To the extent that we are still targeting our efforts through the contract mechanism, I am assured that we are becoming more selective and more exacting.

C. But there is a decided shift from solicited research toward investigator-initiated research in both small and large packages--R01s, P01s.

SLIDE 14 20

XII. The Grant Stabilization Initiative

A. A decisive step in that direction was taken in the late '70s when NIH administrators began to explore approaches to the stabilization of research.

B. Dr. Fredrickson asked the Director's Advisory Committee [May 1979] to consider a policy of stabilizing the competing research project grants--that is, protecting them from perennial oscillations as long-term commitments are honored in times of adversity.

C. In February 1980, testifying before the appropriations subcommittees, he expressed the Administration's desire to hold the competing continuations in 1981 to the 5,000 level, or about one-third of approved applications. We see that the actual number for that year was 5,109.

D. This initiative still receives a high priority, though the projection is only 4,741 for 1982 and 4,100 for '83.

21

XIII. The Future of Stabilization

A. In the face of a shrinking research dollar, we may be approaching limits for stabilization. There may come a point where the effort will have a destabilizing effect on other programs.

B. We are looking at the turnover data in the various award programs to see whether the stabilization targets should be revised.

C. We might need to consider a policy of supporting the competing project grants as a fixed proportion of all awarded funds, rather than a set number.

D. In years of austerity, that might necessitate renegotiation of the noncompeting continuations or reduction of other support. But such a policy would ensure a constant infusion of new investigators and lend greater visibility to the stabilization concept.

SLIDE 15 22

XIV. The Changing P.I. Pool

A. Now I would like to mention briefly a matter of some concern to NIH administrators--the changing composition of the principal investigator pool.

B. This has alarmed Congressional committees and received some publicity.

C. The chart shows a relative decline in the number of M.D.'s newly receiving R01 grants. These dropped from 32 percent in 1968 to 19 percent in 1980. The actual number, however, has remained fairly steady.

D. M.D.'s who also have the Ph.D. increased from 43 to 62.

E. The range for Ph.D.'s entering the system was 402 to 1,231. In 1980 there were nearly four times as many new Ph.D.'s as M.D.'s.

SLIDE 16 23

F. Looking now at P.I.'s on all types of R01s--that is, new, renewals, and noncompeting continuations--we again see that Ph.D.'s are forming an ever larger proportion of the pool. (These grants account for 85 percent of all P.I.'s.)

G. Again there is an increase in the Ph.D./M.D.s.

H. On the other hand, the M.D.'s have decreased in number as well as proportion. There has been a rise, however, since 1978.

I. The situation is at least partly due to the declining success of M.D.'s in obtaining these grants. With the increasing sophistication of research, Ph.D.'s now excell in designing proposals.

J. Other reasons:

- Lack of laboratory experience in medical school.
- Debt load of the M.D. graduate.
- A decline in M.D.'s on NIH training awards. Such training favors success on NIH grants.

K. We should note that many M.D.'s are found on center grants and other awards.

L. On RCPA's, supporting 1,263 awardees in 1981, 44 percent were M.D.'s--up from 33 percent in 1979. The rise is due to the popularity of academic teacher and clinical investigator awards.

M. The New Investigator Award, introduced in 1971, continues to attract M.D.'s and Ph.D.'s about equally. These are junior faculty awards in specific disciplines. The program has grown steadily after a modest start.

N. But there seems to be a downward trend in the proportion of M.D.'s on other R grants (mostly investigator-initiated)--from 79 percent in 1975 to 65 percent in '80.

O. And a slight decline on program projects (P01s).

SLIDE 17 25

XV. The Training Pool

A. A related matter for close attention is the composition of the training pool.

B. The slide tabulates the total number of NIH trainees and fellows from 1969 to 1983 (est.) in terms of full-time equivalents. We see a gradual decline to an estimated low of about half the 1969 level.

C. As part of our stabilization effort, NIH seeks to provide about 10,000 (FTE) positions annually.

D. As you know, the National Academy of Sciences, under the Nation Research Service Award Act of 1974, was asked to advise Congress on the training areas and the number of trainees needed in each. I was privileged to serve on the Academy's committee.

SLIDE 17 (CONT.) 26

E. We recommended that 2,800 postdoctoral positions for clinical research training be awarded annually.

F. At no time have all 2,800 positions been filled--mainly because of a shortage of M.D. applicants.

G. Some may be dissuaded from trying research by the payback requirements. I think the payback may be less of a disincentive to the Ph.D. already committed to research.

SLIDE 18 27

H. As you can see, the number of M.D. postdoctorals utilizing these awards dropped sharply--from about 5,300 to 1,700*. (We have shifted from FTE data to a sum of full- and part-time awards.)

I. Academic postdoctorals overtook the M.D.'s around 1976.

*M.D., equivalent professional, and combined degrees.

SLIDE 19 28

J. This slide focuses on postdoctoral trainees and fellows. You can see the dramatic drop in M.D.'s as a percent of total postdoctorals.

K. This probably reflects a declining interest of physicians in biomedical science careers.

L. There is an increase, however, in total postdoctorals as a percent of total awardees.

M. The Senate reauthorization bill, which has been reported out by the Hatch committee, would drop the payback provision. On the House side, however, the Waxman committee, while strongly supporting NRSA and acknowledging the shortage of clinical investigators, has not yet taken a stand. We are anxious to see what will happen in conference.

LIGHTS

XVI. Advisory Groups in the New Directions

A. Our efforts to maintain excellence and creativity in today's climate place heavy demands on our study groups, advisory councils, and program leadership. Hard decisions must be made on where to place limited resources and how to use them most effectively.

B. Our approaches to the health missions tend to fluctuate between targeted programs (via contracts) and basic science support (via project grants), depending on the state of the art, the perceived values of the various support mechanisms, and the availability of funds. We have seen this at the laboratory level, the Institute level, and the agency level. It is probably consistent with good programming and good science in a mission-oriented endeavor.

C. But program leaders need expert advice in devising strategies and maximizing results. Our study panels and Advisory Councils--the peer review system--will be the key to success in the difficult process of priority-setting and project selection.

D. I have been taking a look at the Director's Advisory Committee with a view to making the most of their valuable capabilities.

- Their most effective role, I believe, is to advise me on specific policy matters under consideration by NIH.
- The issues presented to the DAC will be more focused and will involve the Institute Directors more in policy development.

- For example, I will ask the DAC at the next meeting to examine salary support for professional staff as a direct cost item under research grants. NIH vs. university responsibility is at issue as well as escalating costs.

- I have established an NIH working group to help shape this issue and structure the DAC meeting.

XVII. Conclusions 32

A. The grants and awards system established 38 years ago* along lines laid down earlier in the National Cancer Institute Act has well served NIH and the biomedical sciences generally.

B. I believe it is the best system yet devised for impartially choosing projects and awardees to advance knowledge of biological mechanisms and disease.

C. To operate effectively, the system requires massive, exacting staff work under competent leadership.

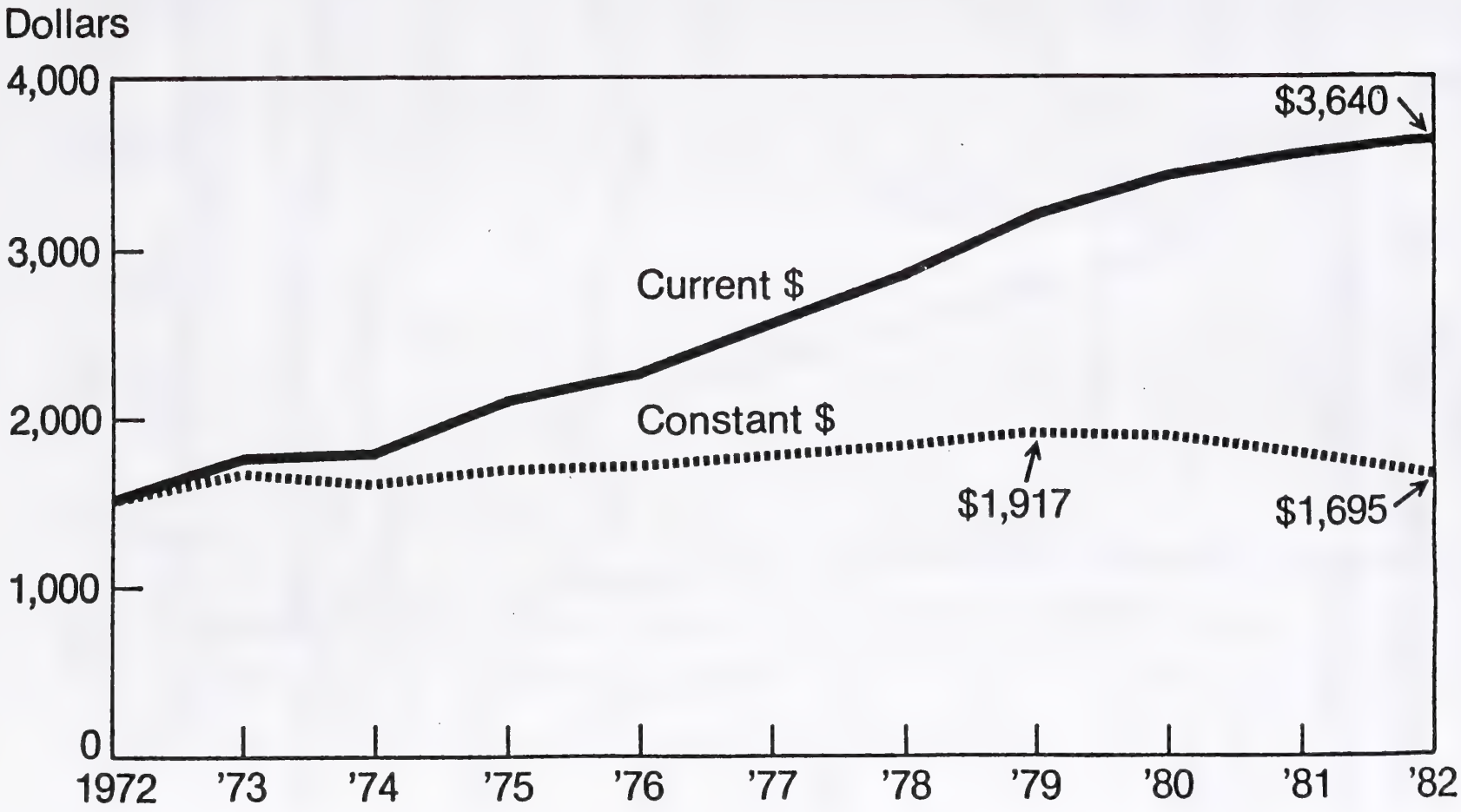
D. I want to leave you with the strong impression that I have every confidence in both the system and its extramural NIH framework. In the difficult times ahead, they will continue to meet their high standards, in the all-important selection of people and projects to improve health through discovery.

*PHS Act of 1944 [P.L. 78-410, Sect. 301(d)]

SLIDE 1

Total NIH Appropriations, 1972-82

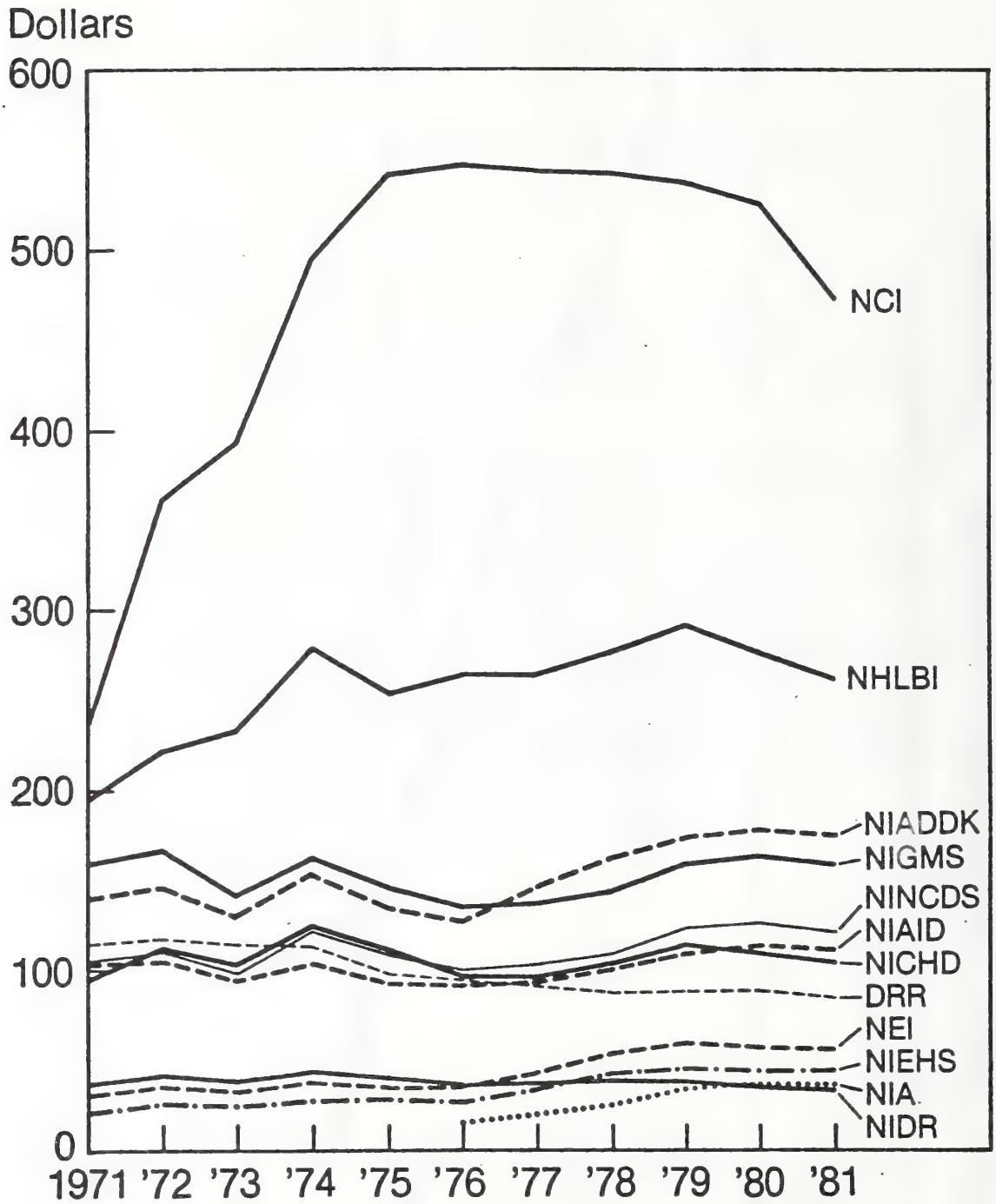
In Current and Constant Dollars (Millions)



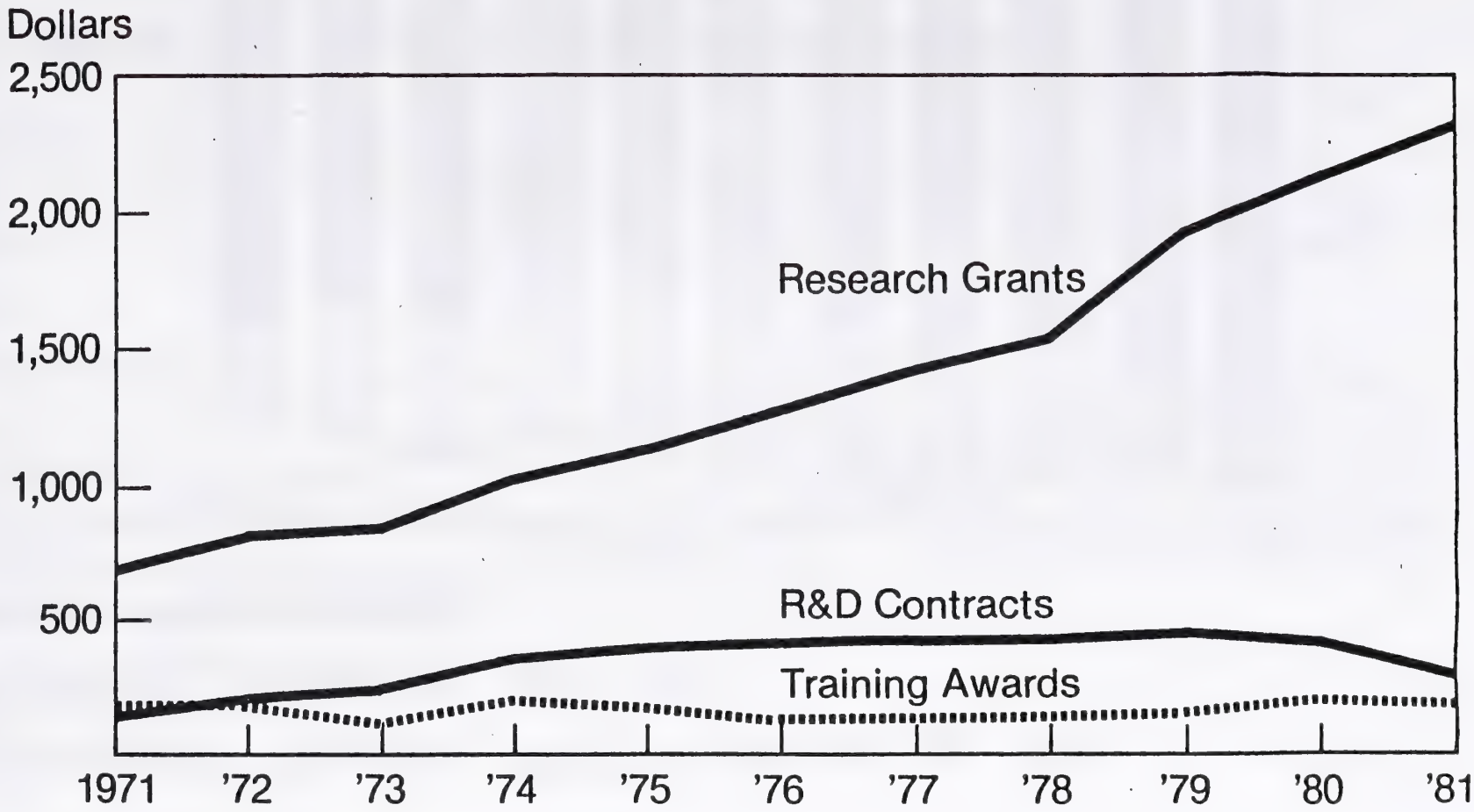
SLIDE 2

Annual Obligations by NIH Component, 1971-81

In Constant Dollars (Millions)



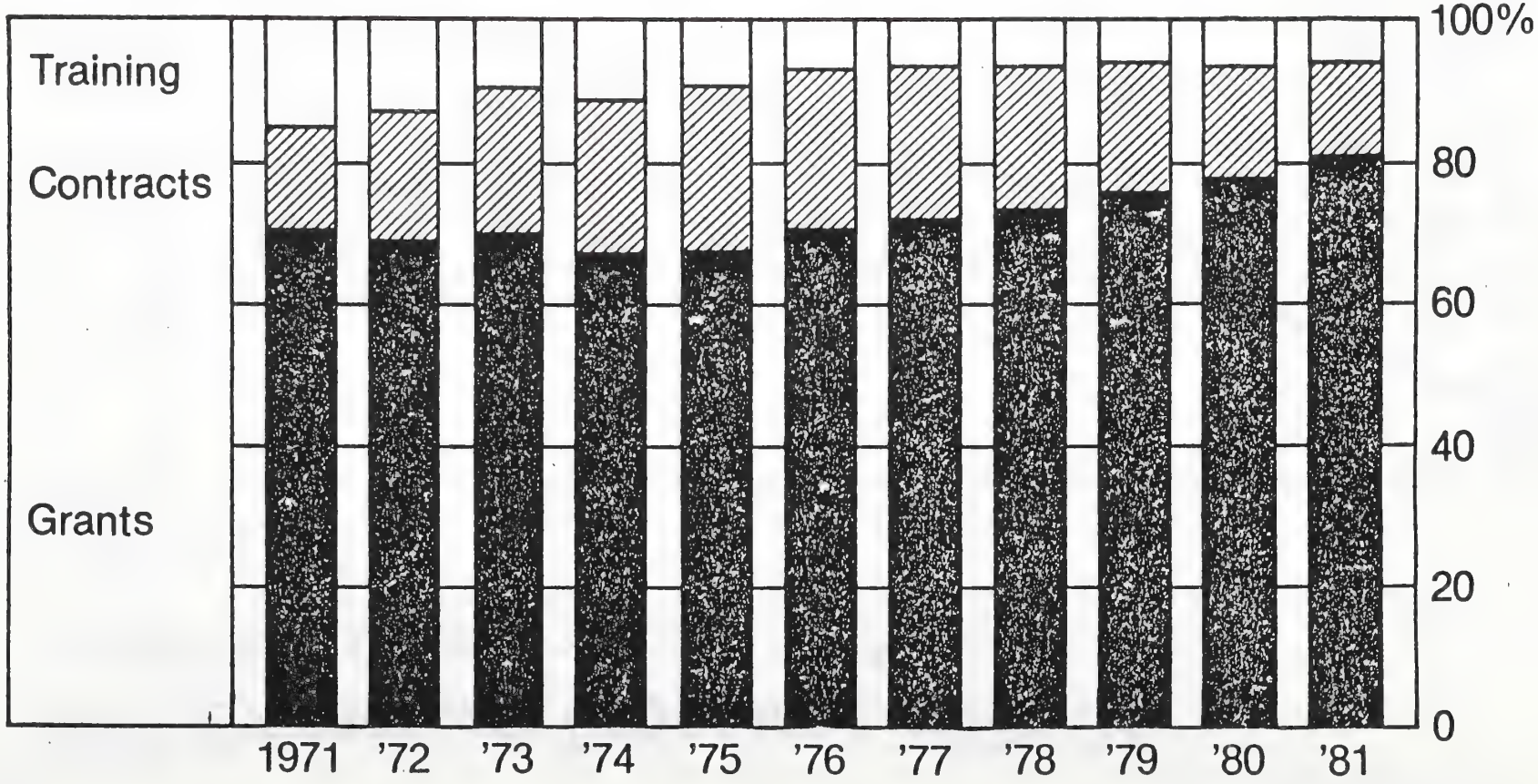
NIH Extramural Programs, 1971-81
(Millions of Dollars)



SLIDE 4

Research Grants, R&D Contracts, and Training Awards, 1971-81

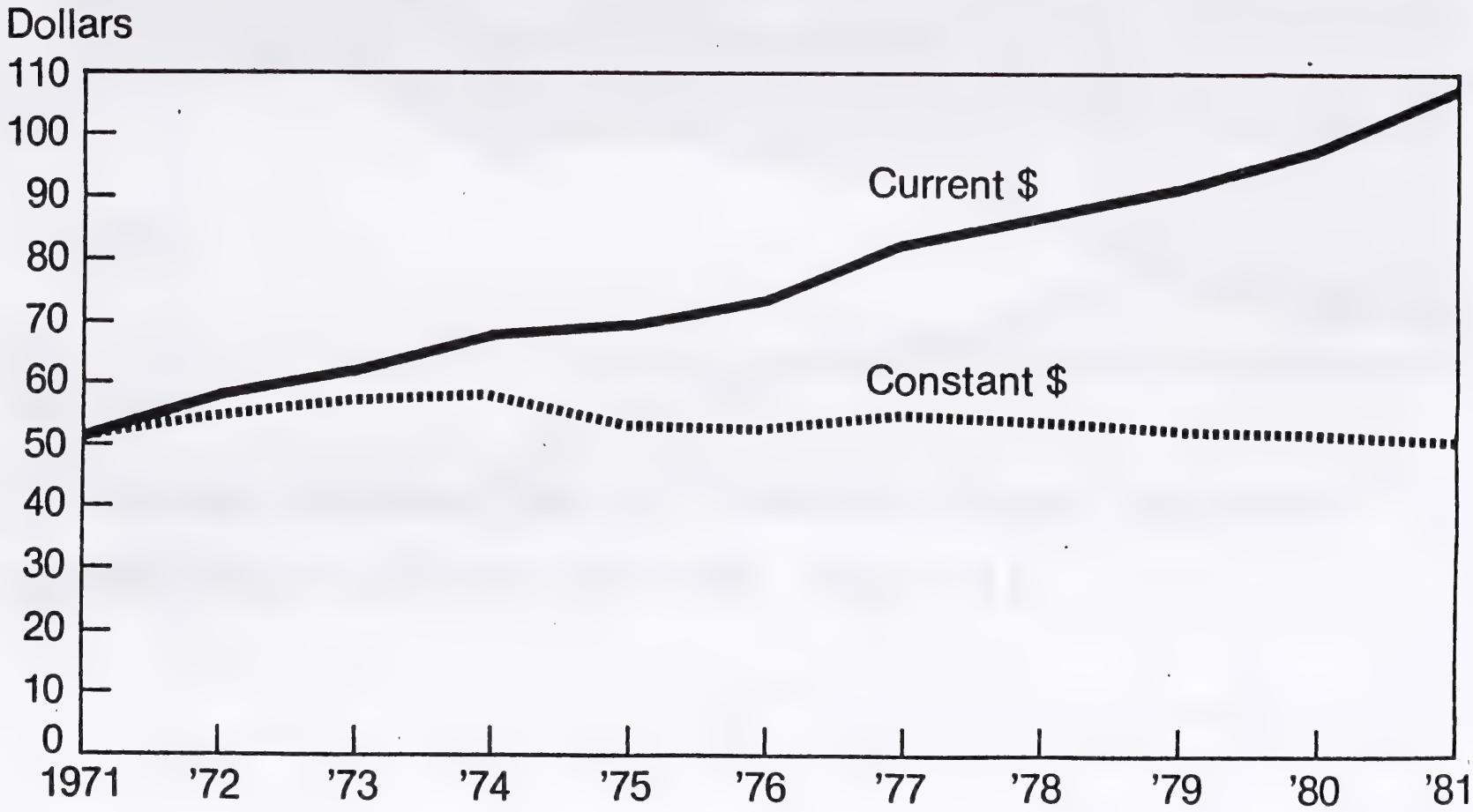
Shown Proportionally



SLIDE 5

Average Research Project Grant, 1971-81

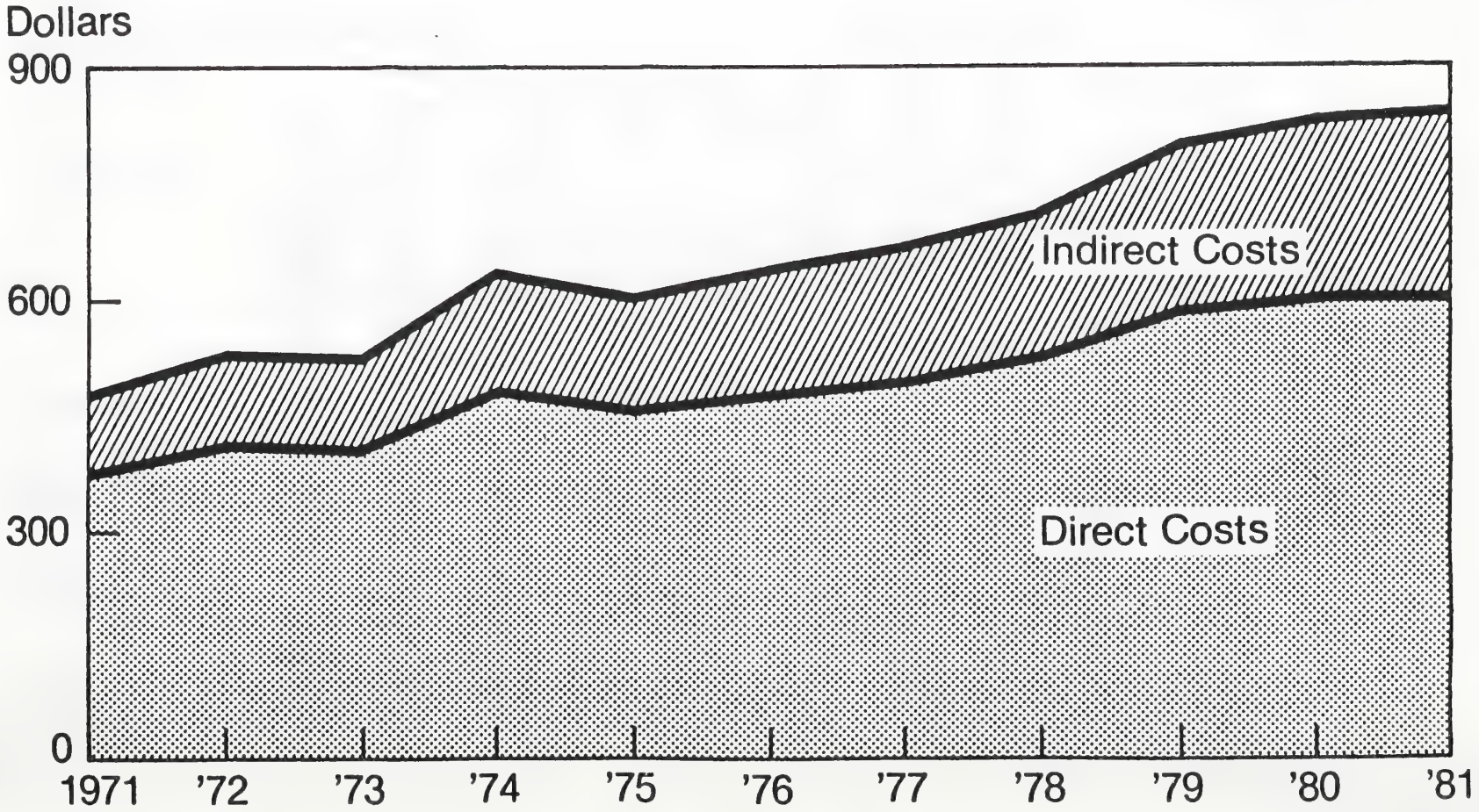
In Current and Constant Dollars (Thousands)



SLIDE 6

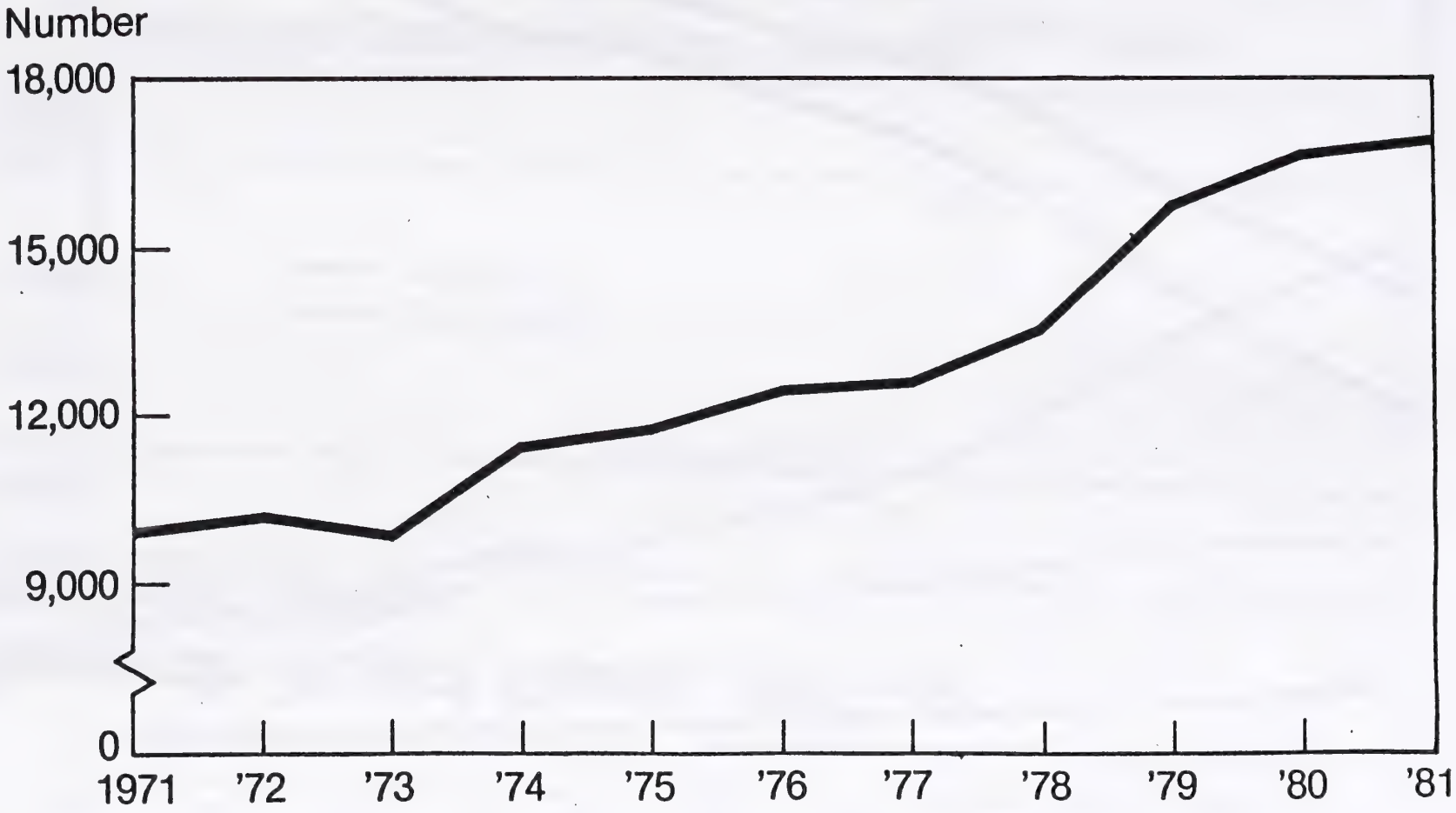
Research Project Grants, 1971-81

Direct and Indirect Costs in Constant Dollars (Millions)

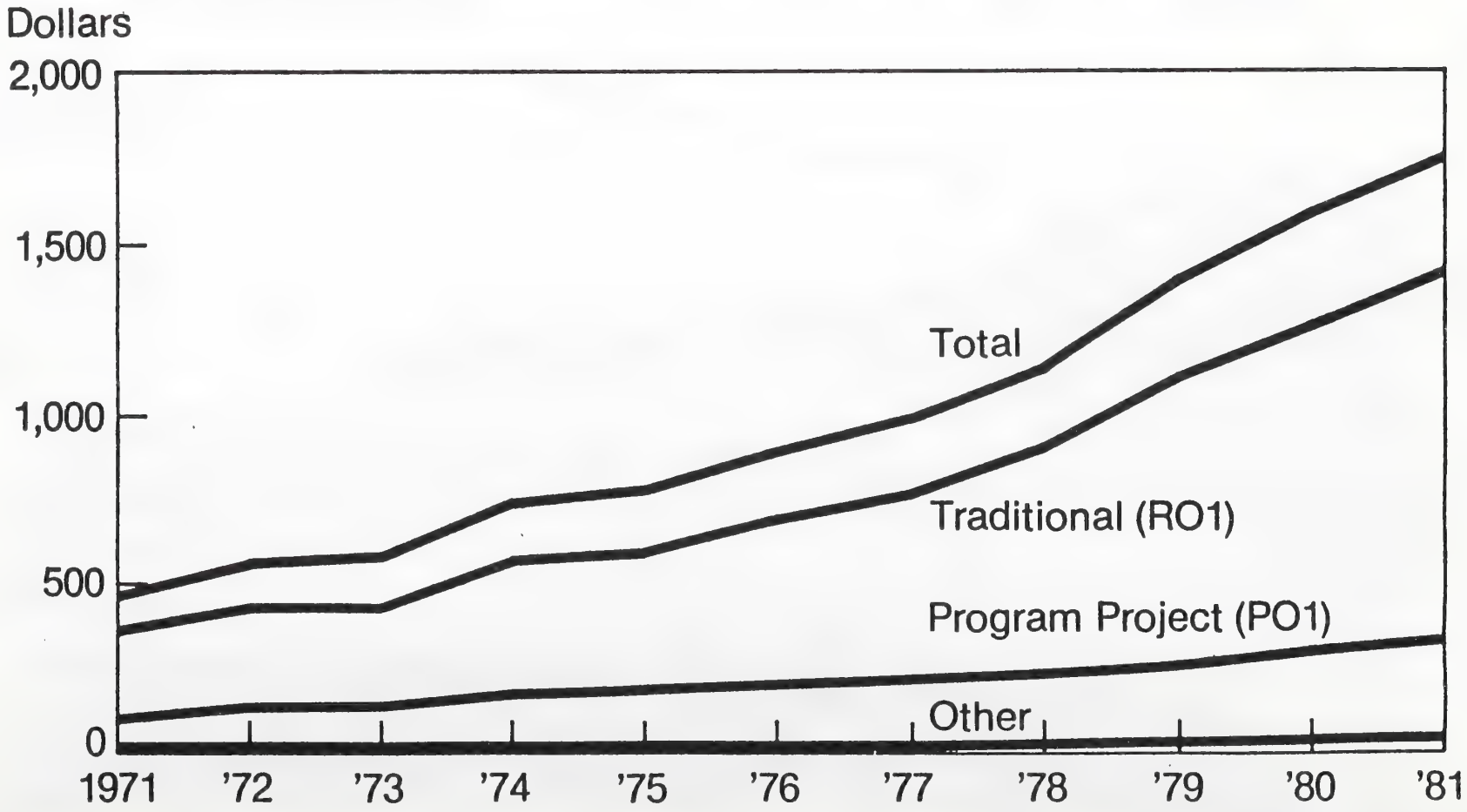


SLIDE 7

Number of Research Project Grants, 1971-81

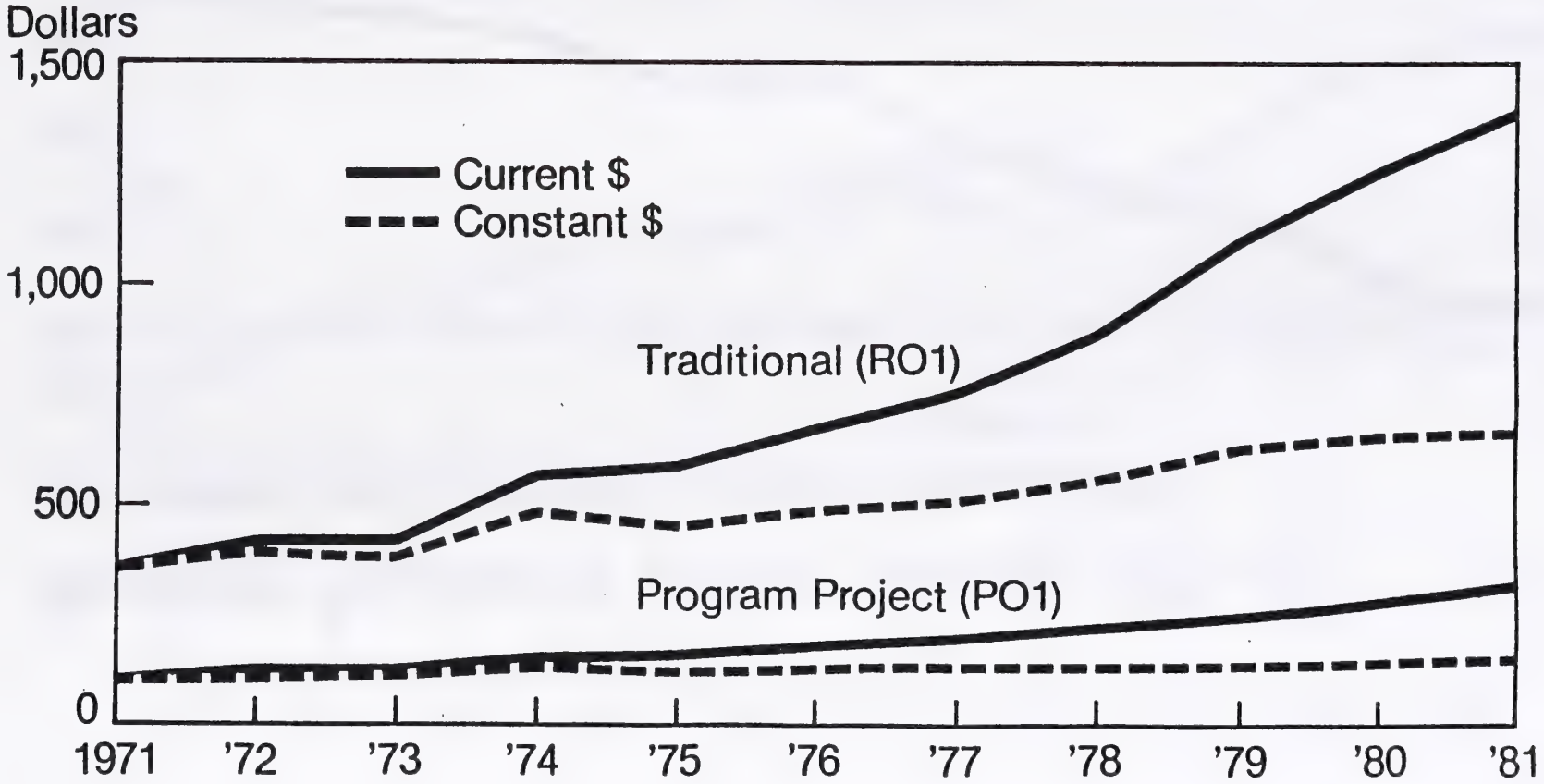


Research Project Grants, 1971-81
(Millions of Dollars)



Research Project Grants, 1971-81 — Traditional and Program Project

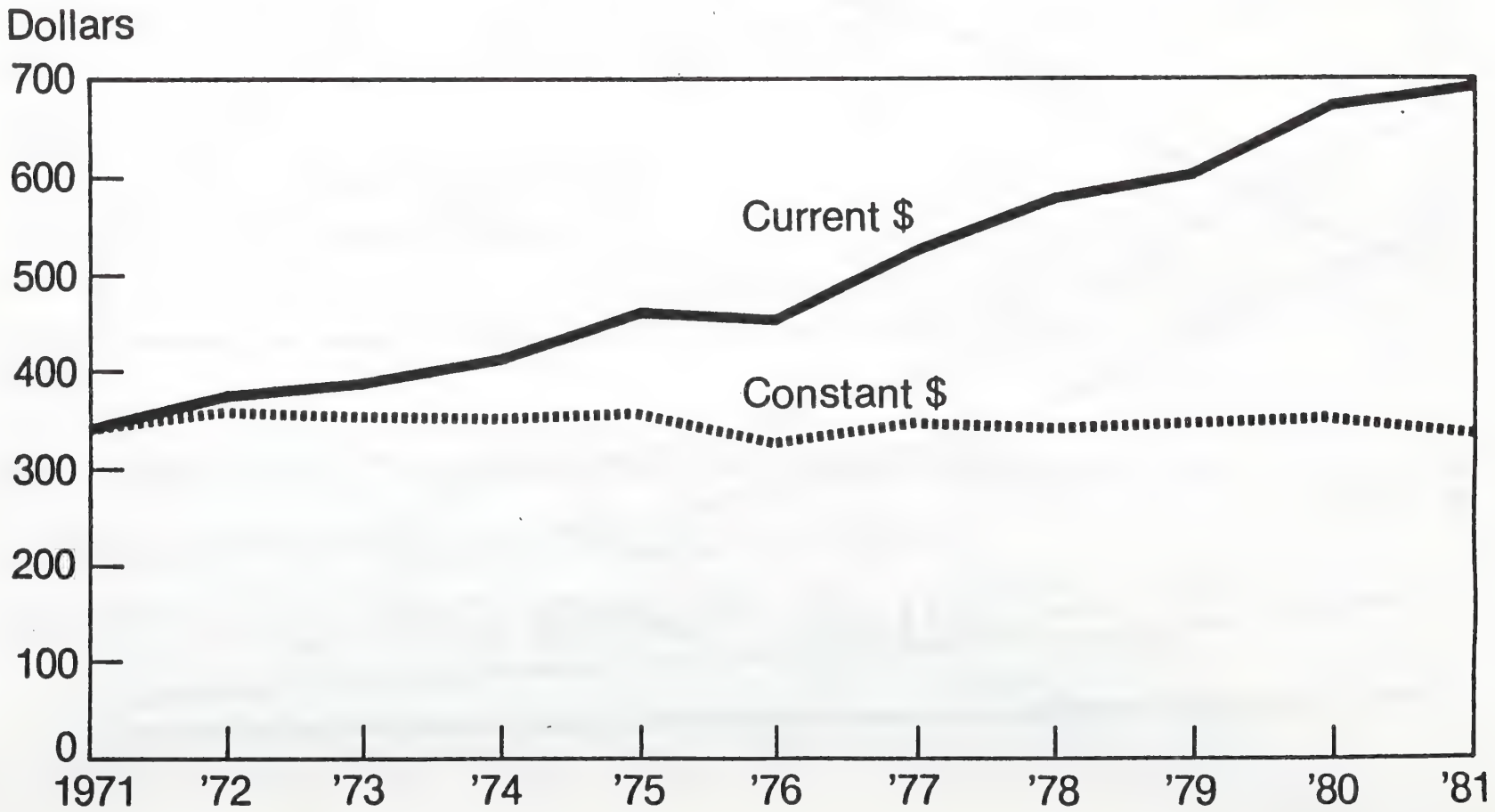
In Current and Constant Dollars (Millions)



SLIDE 10

Average Research Center Grant, 1971-81

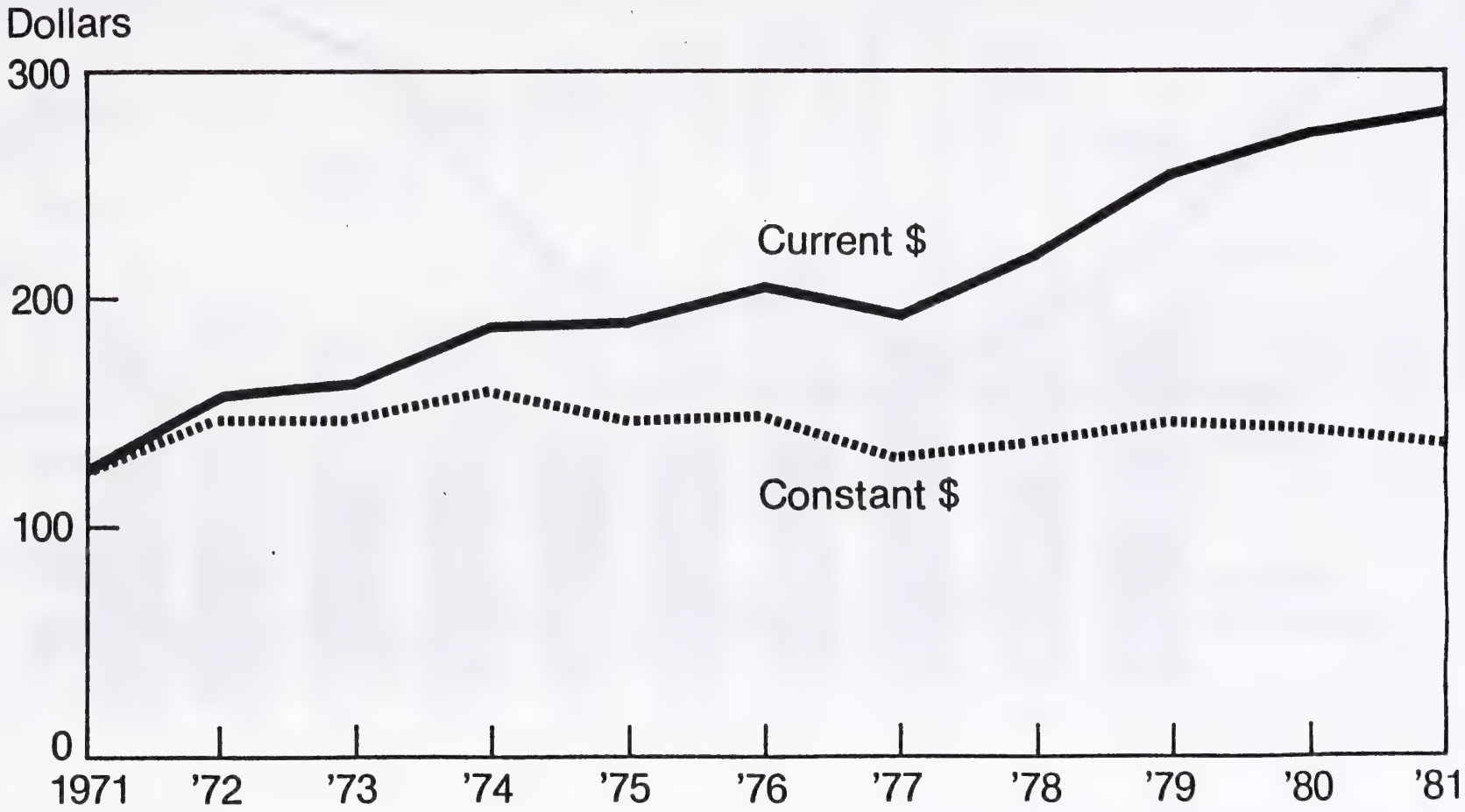
In Current and Constant Dollars (Thousands)



SLIDE 11

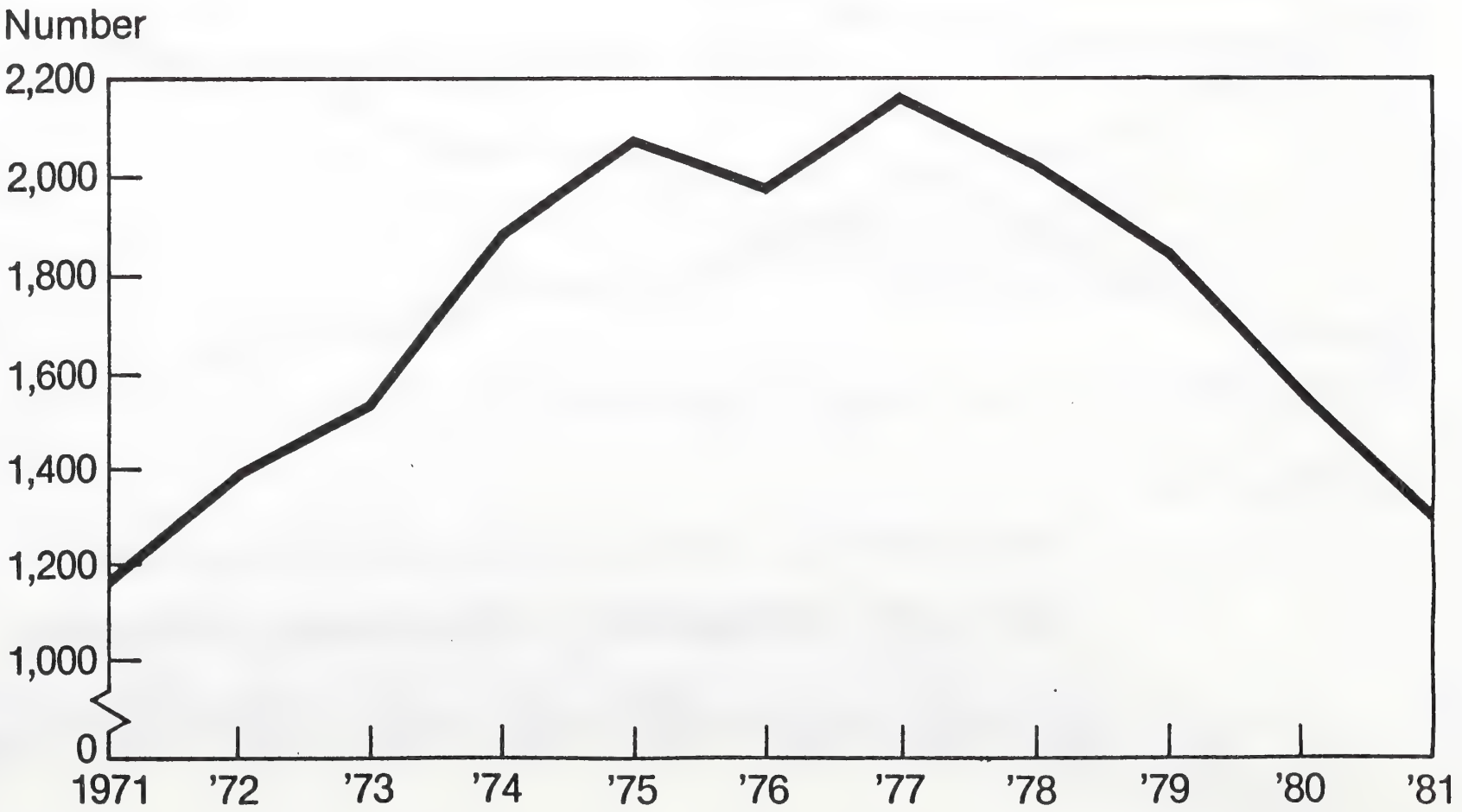
Average Research Contract, 1971-81

In Current and Constant Dollars (Thousands)



SLIDE 12

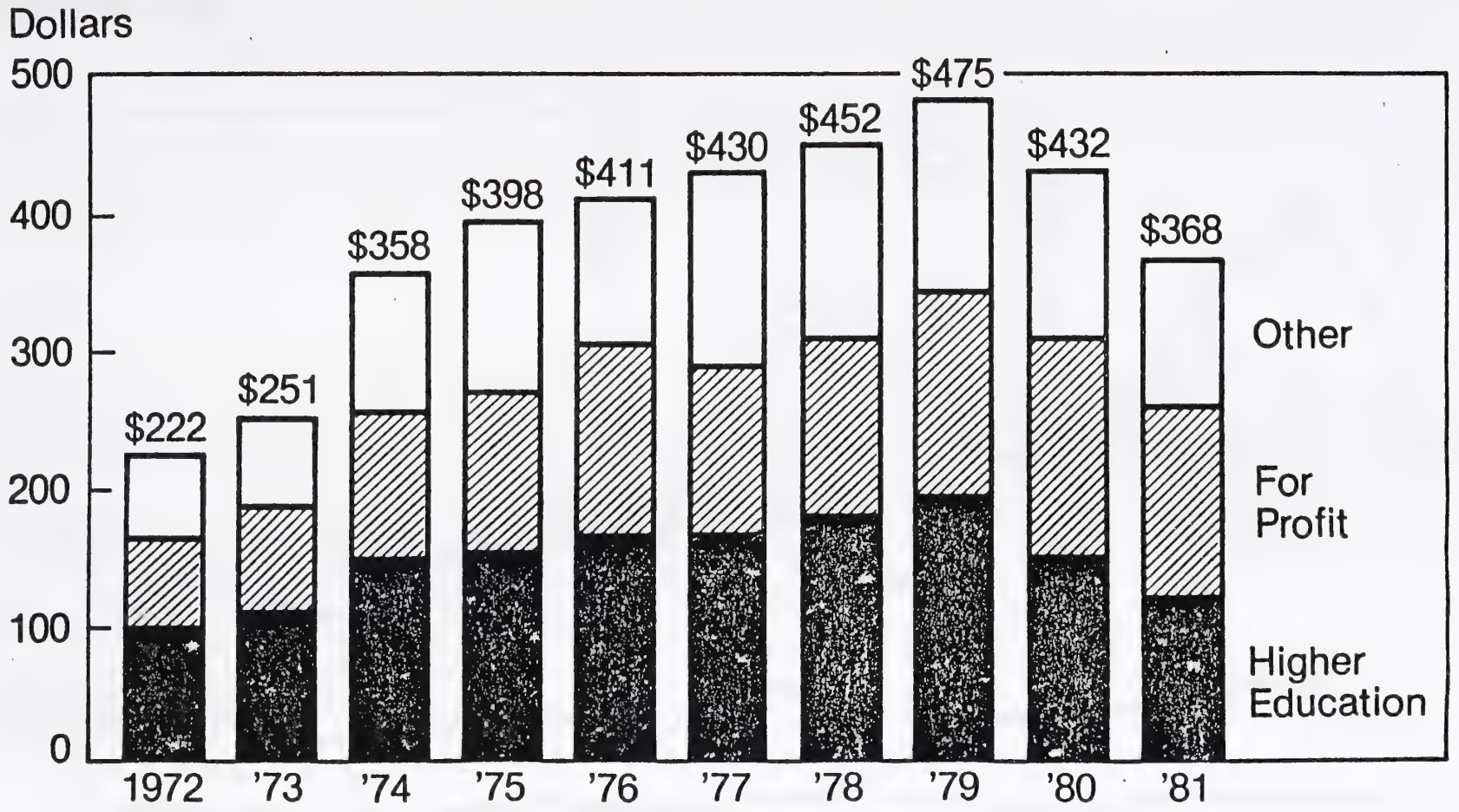
Number of Research Contracts, 1971-81



SLIDE 13

R&D Contracts by Performer, 1972-81

(Millions of Dollars)



SLIDE 14

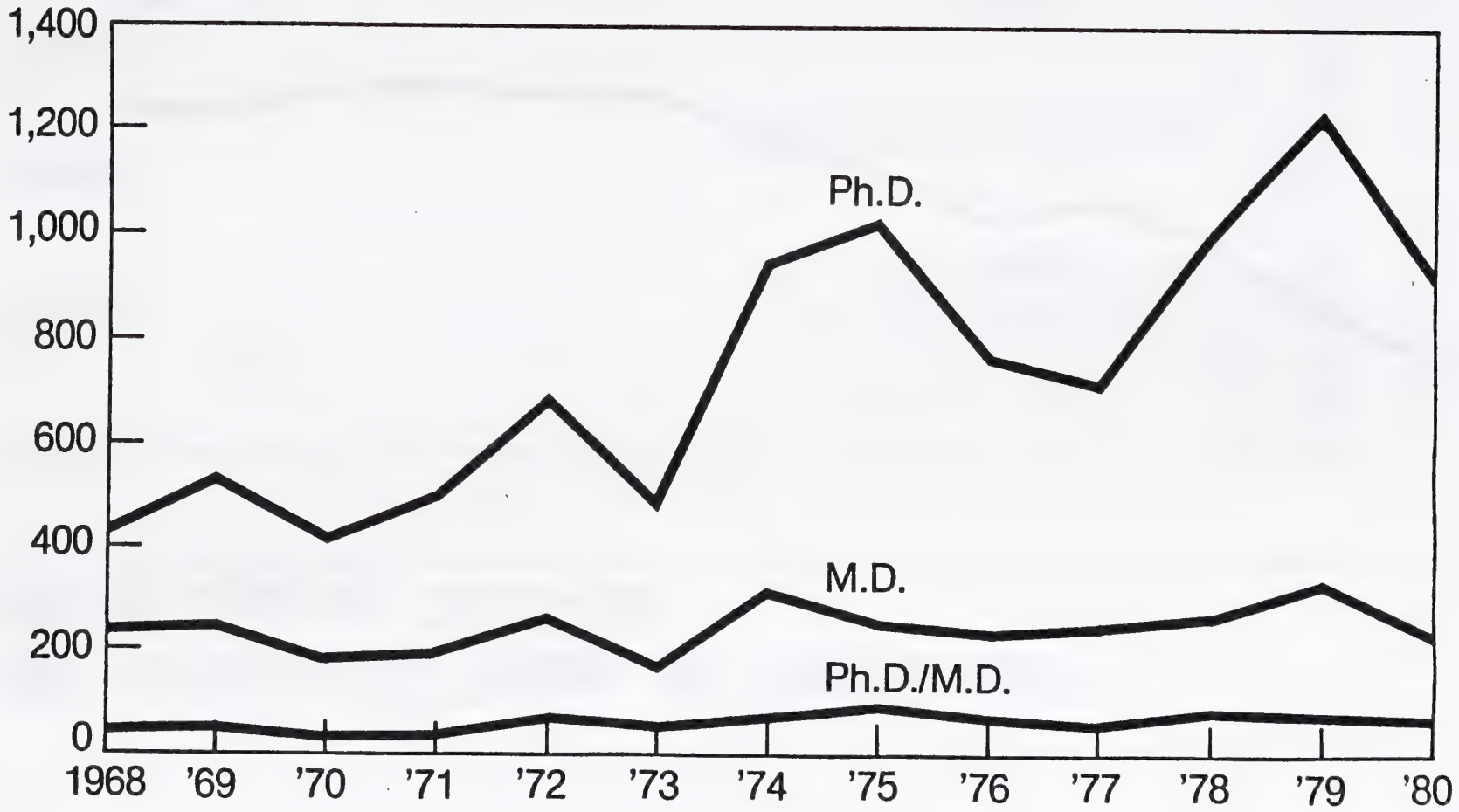
RESEARCH PROJECT GRANTS
New Awards and Competing Renewals
1977-1983

	No. of awards	$ in millions
1977	3,840	$306.9
1978	5,200	420.9
1979	5,944	525.5
1980	4,785	472.5
1981	5,109	545.0
1982 est.*	4,741	527.6
1983 est.**	4,100	492.3

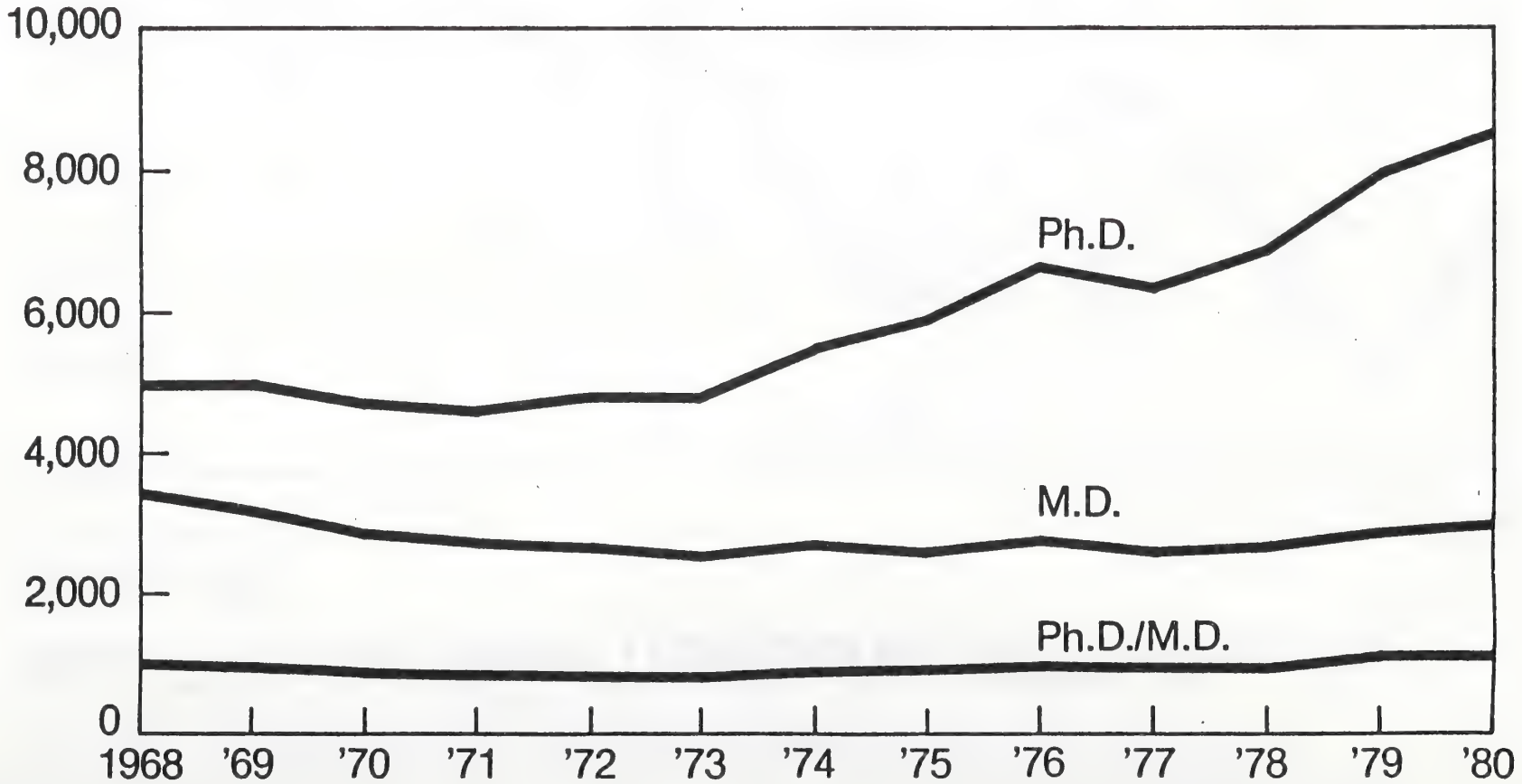
*Based on Cont. Resol. (P.L. 97-161).
**Based on President's Budget.

SLIDE 15

New P.I.'s on New Traditional (RO1) Grants, 1968-80



All P.I.'s on All Types of Traditional (RO1) Grants, 1968-80



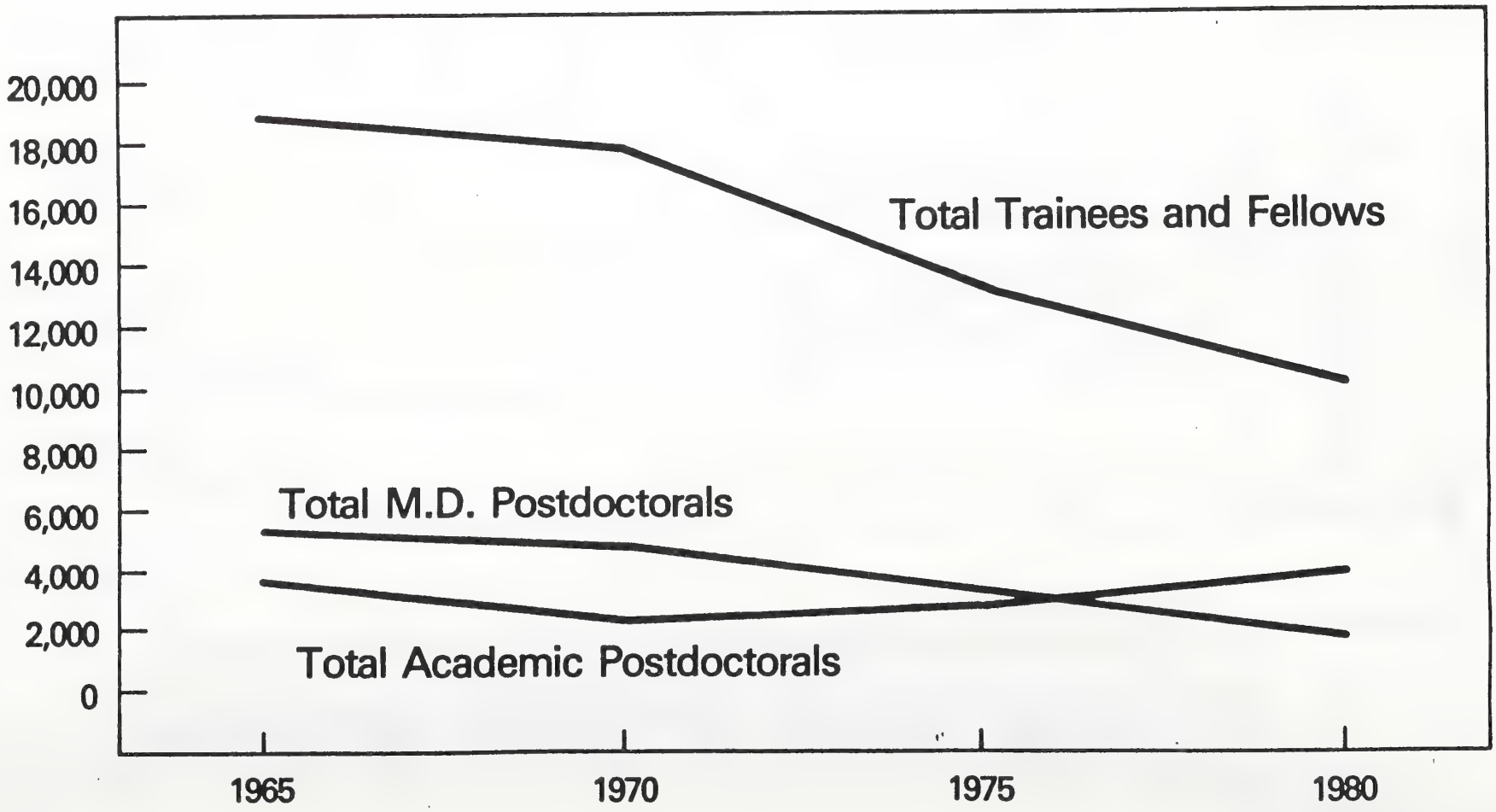
SLIDE 17

NUMBERS OF TRAINEES AND FELLOWS
ON NIH RESEARCH TRAINING AWARDS
1969-1983 Est.

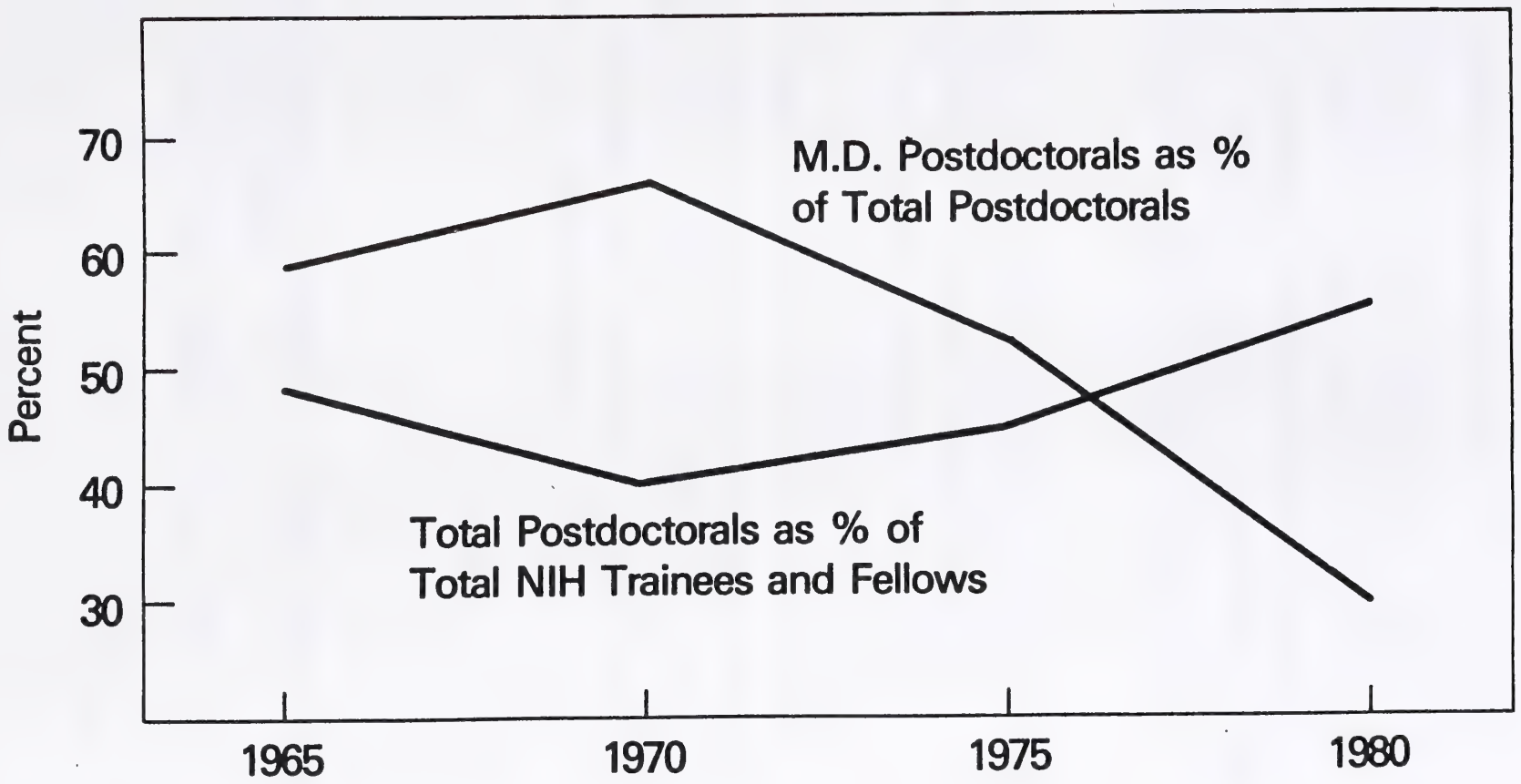
(Full-Time Equivalents)

Year	Number
1969	16,138
1970	14,810
1971	14,288
1972	14,613
1973	12,675
1974	13,547
1975	12,272
1976	9,654
1977	10,198
1978	11,123
1979	11,197
1980	10,664
1981	10,695
1982 Est.	9,702
1983 Est.	8,915

NUMBER OF TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1965-1980



POSTDOCTORALS AS PERCENT OF TOTAL NIH TRAINEES AND FELLOWS, AND M.D. POSTDOCTORALS AS PERCENT OF TOTAL POSTDOCTORALS 1965-1980



SELECTING PRIORITY AREAS FOR RESEARCH*

by

James B. Wyngaarden, M.D.**

I am aware that I am speaking today to a well-informed audience of able advocates. Through your research and personal experience, I am certain that you have learned as much as anyone about neurological and communicative disorders. I salute you for your dedication and your determination to advance research that will one day provide answers to the health problems of your concern.

You are familiar, I am sure, with the first-rate and highly promising research conducted and supported by the National Institute of Neurological and Communicative Disorders. Since I don't believe there is much point in preaching to the choir, I am not here today to tell you what you already know. Because I am new to most of you and to the National Institutes of Health, I thought I would discuss with you some of my views--about NIH and its mission; about priorities and the management of NIH programs and research in general; and, finally, some thoughts about the future of biomedical research and its potential--especially in the neurosciences.

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*Presented at the annual meeting of the National Committee for Research in Neurological and Communicative Disorders, Twin Bridges Marriott Hotel, Crystal City, Virginia, October 2, 1982.

**Director, National Institutes of Health, Bethesda, Maryland 20205.

First, I want to acknowledge the work of two people with whom I am certain you are all familiar--Drs. Murray Goldstein and Katherine Bick, Acting Director and Deputy Director of NINCDS. They have made important contributions to the progress of research programs of the Institute and to NIH. They have provided strong leadership during their lengthy terms in an acting capacity and in prior service. I am pleased to have this opportunity to commend them publicly for their stewardship and dedication.

As you know, the search for a permanent Director of NINCDS was re-opened earlier this year. I am currently reviewing the candidates and expect to announce a new Director within the next few weeks. While I can't give you a name today, I can assure you that the individual selected will be highly capable, informed, and dedicated to the research programs of the Institutes.

Mission of the NIH

Within our budgetary boundaries, we will vigorously pursue the mission of NIH which can be stated simply: "to uncover new knowledge that will lead to better health for everyone." Through the years, that fundamental charge has been re-stated many times by Congress in several Acts that modified and expanded the responsibilities of NIH. Congress has also repeatedly expressed its belief in the benefits of biomedical research. That confidence has resulted in a multi-billion-dollar investment which, over the years, built a biomedical research capacity second to none. It is a source of national pride and international prestige. As Director of NIH, I felt a personal responsibility to make every effort to maintain the proud tradition of service

established by NIH, to encourage the creativity of scientists, and to sustain the high quality of their research. The Nation and the world will continue to enjoy the benefits of that effort.

The Federal role in biomedical research, expressed through NIH, is central and essential, but there is no Federal monopoly on health research. In speaking of the Nation's research capacity, I include laboratories in publicly supported and private colleges and universities and in industry. And, most assuredly, I include the valuable contribution of the voluntary sector, of which NCR is an important member. The unified and deep concern of your broadly representative organization is an inspiration to all who work to prevent and treat disease and disability. Your support of research contributes directly to the progress and achievements of medical science.

We depend heavily on the public and the scientific community. For example, while NIH operates a large program of laboratory and clinical research in its own facilities, four-fifths of our expenditures go to the support of biomedical research conducted in universities, private laboratories and elsewhere. From the beginning, the main NIH mechanism of research support has been individual project grants for studies proposed by non-Government scientists. About half of the NIH budget currently supports such investigator-initiated projects.

NIH programs express national policy shaped by Congress through the years. That policy, which I fully endorse, encourages diversity and excellence in health research; it relies on the scientific community to identify, through a

competitive peer review process, the ideas and investigators most worthy of support. The public view, expressed by organizations such as yours, is another important factor in the shaping of national research policy. Emphasis on the individual, helps to assure that public funds invested in biomedical research support the most creative ideas and energies in the American health research community. The shaping of NIH itself is a commentary on our national health policy--it responds to needs and opportunities as perceived by diverse groups within and outside the Government.

Some Fundamental Concepts

In pursuing our over-all research mission, we must continue to rely heavily on three fundamental concepts--the importance of basic research, the value of investigator-initiated research, and the need to train new scientists.

The fundamental approach to discovery at NIH continues to be through support of investigator-initiated basic research into the life processes. Biomedical science is increasingly probing the cellular and molecular levels of function. Nowhere is this more true than in research conducted and supported by NINCDS. And that is to be expected, because the disorders about which you are concerned are among the most baffling that face medical science today. It is through basic research conducted by creative individuals, I believe, that we will someday solve the mysteries of the brain and the nervous system. A corollary to the investigator-initiated approach is the need to assure a continuing supply of well-trained scientists to carry out the research needed to meet our objectives. There is a close relationship between the continued

productivity of research and the replenishment of the supply of qualified investigators.

It is useful to think of research as a continuum stretching from investigations into the most fundamental mysteries of nature to programs designed to translate and then transfer new knowledge to the practicing physician. It is in terms of that continuum that we must establish priorities in NIH programs and activities. In addition to our primary research mission, as you know, we engage in a variety of other activities, such as clinical trials and investigations to test new medical technologies, drugs and devices, in community education and demonstrations, and the in development of orphan drugs.

Setting of Priorites

Within that range of responsibilities, you can appreciate the extreme difficulty of establishing priorities and allocating support. When it comes to health and life-threatening disorders, all areas are "first" priorities. Nevertheless, hard choices must be made and research managers must gather information from all posible sources, weigh the data carefully, and then seek to make sound decisions. It is an emotionally and physicially draining experience.

The ultimate goal of biomedical research is the elimination of disease and disability. To prevent disease, we need to know the process--how the disease acts, and its target in the body. Sometimes we are fortunate, as in the case

of polio vaccine, where a confluence of factors plus a determined public health effort removed almost overnight a cloud that had hung over society for many years. That kind of conquest of disease is rare. Most often we slowly amass evidence and carefully look to place each new piece of information in a giant puzzle. In the process, new opportunities appear and lead us in previously unforeseen directions.

Essential to decision-making on research priorities is the availability of a critical mass of basic knowledge with which to launch further inquiries. All research planning proceeds from what is known about a health problem, life process or disease area. Such a review helps to identify scientific opportunity, gaps, and needs. Also assessed are potential interventions ready for clinical testing and approaches or emphases required to expande the knowledge base further. Closely allied, of course, is a consideration of the existence of adequate research resources, especially important in modern biomedical research which demands sophisticated equipment and instrumentation.

The selection of priority areas for clinical research depends on assessments of:

--The physical, emotional, societal, and economic costs of various diseases.

--The readiness of the state of knowledge for application to disease prevention or treatment.

--The potential impact of various research strategies on reducing the burdens of disease.

The impact of some diseases, such as cancer or cardiovascular disorders, on national and international health is of such dimensions as to warrant high priority. Other diseases, however, merit high priority because they provide unique research opportunities despite their relatively low prevalence or limited geographic distribution. These comparatively rare diseases may have well-defined metabolic or genetic characteristics that make it possible to study underlying mechanisms that also occur in more prevalent diseases but are masked by complicated changes.

An interesting example is Huntington's disease, a genetic disorder of low prevalence in the United States which has been accorded priority by NINCDS. The disorder is being studied in collaboration with scientists at a university in Maracaibo, Venezuela. A population of 200 patients descended from a Spanish sailor who arrived in the country in 1960 provides a unique opportunity to study an inherited disease with neurologic manifestations similar to those in Parkinson's disease. This is a valuable approach because the neurologic manifestations of the more prevalent Parkinson's are less well-defined than those in Huntington's disease.

Another area that receives special attention at NIH is the development of "orphan" drugs. NINCDS, as you may know, is cooperating with the pharmaceutical industry to develop and evaluate needed new orphan drugs in the area of epilepsy. This arrangement will be further explored this year in hopes of expanding the program to other incapacitating neurological and communicative disorders. A further development in this area is creation of the Orphan Products Board established by the Department of Health and Human

Services under the Chairmanship of Dr. Edward N. Brandt, Assistant Secretary for Health. NIH, along with other HHS agencies, is a member of the Board which, among other things, identifies orphan products that need developmental or other assistance in order to secure marketing approval. As part of its objective or stimulating orphan product research, development and marketing, the Board will encourage private initiatives and Government effort where appropriate.

I want once again to emphasize the importance of the views of professional societies and voluntary health organizations in the planning and priority setting process at NIH. Such views are sought at gatherings like this, for example. But we also employ more structured means such as national advisory councils, special groups or task forces and commissions that consider specific research areas or health problems.

Finally, of course, there is a comprehensive and highly organized process for setting priorities within each Bureau, Institute, and Division of NIH. The priorities are eventually integrated within the Director's office as part of the annual budget process.

It is difficult to overstate the complexity of this process because in so many instances there are dichotomies for which cogent arguments can be made for either alternative. For example:

--Investigator-initiated vs. mission-oriented research. The value of the former is well accepted, but when important questions about disease are not being addressed the program planner must correct the imbalance.

--Prevention vs. treatment of disease. The thrust toward preventive studies today must not obscure the need to improve the management of non-preventable diseases or to treat those persons who have acquired preventable disorders.

--Basic vs. applied research. There is no lack of advocates for basic research and no dearth of evidence of its value, but this should not obviate the need for technology transfer and the development of new approaches to improved diagnosis and therapy.

Although one cannot plan a discovery, one can attempt to identify, through sufficient expert input, those scientific areas likely to yield beneficial results. Plans must, however, be flexible and able to accomodate the unexpected. A plan is not an absolute blueprint, but it does establish goals and objectives toward which scientific workers can strive, and it can aid in the assignment of priorities for the optimum use of research resources.

A Look Ahead

In closing, I would like to emphasize my view that the future looks bright for continuing rapid progress in biomedical discovery. This optimism is based on the recent record of achievement and it is fueled by discoveries that enable scientists to study the inner secrets of like in a way we could not imagine even a few years ago. The main challenge facing health research policy makers and administrators is to maintain a vigorous level of national research capabilities at a time of limited resources. It is important that we exploit the exceptional scientific opportunities presented by what is called "biological revolution."

There is a momentum in science that moves the field in certain directions as areas of high promise are revealed. Some of these areas today are:

--Immunology, virology, and the exploitation of monoclonal antibodies. The therapeutic implications of this field are enormous and potentially include cancer, arthritis, allergies, multiple sclerosis, viral illnesses, and organ transplantation.

--Genetics, gene and enzymes regulation, and recombinant DNA. Here, too, there is broad potential in genetic diseases, toxicology, cancer, and the production of hormones and vaccines.

--Non-invasive imaging techniques, such as Positron Emission Transaxial Tomography (PETT) and Nuclear Magnetic Resonance (NMR) Imaging. These techniques promise to reveal not only anatomical changes, but biomchemical and physiological abnormalities as well, a dimension in diagnosis hardly imagined until recently.

--Receptor site defects and mechanisms of action of hormones and neurotransmitters. Therapeutic implications are again very broad.

--Neurobiolgy, brain function, and neuropeptides. Extraordinary advances in the past decade show promise of providing improved therapy for a wide range of disorders.

You can readily recognize that, virtually all of these promising areas--especially neurobiology--have implications for the wide range of disorders of concern to NCR. The past decade has seen a quantum jump in our knowledge of neurobiology that holds promise for advances in the approximately 600 diseases within the purview of NINCDS.

Because so many of these diseases will be defeated only through greater understanding of fundamental processes, the basic research conducted through other Institutes can also be expected to contribute to progress.

There is now a better understanding of the function of the brain and central nervous system in health and disease. The discovery of the slow viruses that

cause significant neurological damage has been a major advance. Methods of opening the blood-brain barrier selectively have been identified and are being investigated to allow enzyme replacement in certain genetic diseases. Advances in microsurgery have greatly improved the outlook for patients with certain neurological conditions, including brain tumors, and acoustic neuroma. New diagnostic tools including computerized axial tomography (CAT), positron emission transaxial tomography (PETT) and, most recently, nuclear magnetic resonance (NMR), allow detailed imaging of the living human brain and its functions and promise to uncover a wealth of knowledge. Work on neurotransmitters has produced the L-Dopa treatment for Parkinson's disease. These examples are only a small part of the numerous advances made in recent years.

I agree with the many scientists who believe that we have reached a point where revolutionary discoveries in neurobiology will soon be made: There is a readiness for discovery in this field; the critical mass of basic knowledge I mentioned earlier as necessary to advance appears to be available in this area. Continued support for basic, applied, and clinical neuroscience and communicative science will allow us to make the breakthroughs we all seek in these still intractable disorders. While the answers are not in hand and their solution cannot be predicted, I am optimistic about prospects for achievements in neurological and communicative disorders in the decade ahead.

TRENDS IN NIH SUPPORT OF RESEARCH*

by

James B. Wyngaarden, M.D.**

No one attending this Research Week Program needs to be persuaded of the importance of biomedical research to society or to the academic health center. Examples abound to document the relief from suffering that has resulted from the application of research advances. Although accurate figures are not available, it is clear that certain health care costs have decreased because of prevention strategies born of research. Students, faculty, and others can readily appreciate how the curiosity and critical inquiry of research enhance the teaching and health care environment at an institution such as this one. The auditorium in the Clinical Center at the National Institutes of Health has a quotation engraved in the marble wall at its entrance, a quotation from its first director, Dr. Jack Masur, for whom the auditorium is named, that beautifully captures this concept: "Hospitals with long traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching; teaching lifts the standards of service; and service opens new avenues of investigation."

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*Keynote address, Research Week, University of Kansas Medical Center, Kansas City, Kansas, on October 4, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

The support of research has long been a high priority of the Federal Government. The Congress has funded NIH very well over the years, even in the current climate of fiscal austerity and, in January, in his State of the Union Address, the President pledged to increase the NIH budget $108 million.

When policy makers talk about "the Government commitment to biomedical research," they are speaking about the Federal-academic partnership that has been so productive over the past three decades. The partnership represents a shared responsibility to create an environment conducive to the work of scientists. And "research week" is an excellent opportunity to reflect on what this entails for each member of the partnership-- for the Government (NIH) and for the institution itself.

This partnership in the field of health research is of recent origin, having evolved much later than Federal support of agricultural research at land-grant institutions that began in 1887. But the growth of Federal support of biomedical research in academic institutions has been so rapid in the past 40 years that this branch of science now receives almost half of all Federal research and development funds awarded to universities, colleges, and nonprofit laboratories.

It is interesting to look back on the origins of this partnership--for example, a report written in 1945 titled "Science--the Endless Frontier,"[1] by Dr. Vannevar Bush, the President's science advisor. This visionary report did not foresee the magnitude of our current budgets for biomedical research (Bush estimated that perhaps $5 million a year might be adequate) nor did it fully presage the budget difficulties that confront us today. But it did outline the principles for Federal support of health research that have served the national

interest so well in the succeeding years. The flavor and substance of the document stand up well when viewed from the perspective of nearly 40 years. One passage aptly defines our current partnership:

> "The publically and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge...."

Thus, Bush identified the university as the appropriate environment for research and advised against reliance on the free-standing research institute as the dominant mechanism for meeting the Nation's needs. Indeed, it is difficult today to imagine the configuration of NIH or the state of health-related academic institutions had some alternative recommendation been followed.

During most of the history of the NIH, certainly for the past 10-15 years, about four-fifths of the agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. A large portion of that support goes to academic health centers for the compelling reason that you have a national resource for which there is no substitute--your faculties of trained basic and clinical scientists. And further, one of your central purposes is to insure the continuing renewal of that precious resource--the trained investigator.

The mandate of NIH is to conduct and support research, but in order to do this it must also be concerned with the well-being and stability of the research institution. The two elements, support of research and the health of the research institution, are inseparably linked one to the other. To put it even more strongly, the Federal Government--NIH--in carrying out its research mission is, in fact, dependent upon the institution. Our concern is enhanced today as institutions are contending with an array of troublesome issues: philanthropy on the wane, the disappearance of construction grants, and reductions in reimbursement for patient care.

When Bush focused on the university/academic health center as the proper environment for the pursuit of biomedical science, he clearly did so because he recognized that at the crux of the scientific research undertaking is the individual scientist housed at the institution.

He recognized that apart from teaching, a primary obligation of the medical school and universities is to continue the traditional function of such institutions--namely, to provide the individual worker with an opportunity for free study of nature, in the directions and by the methods suggested by his or her interests, curiosity and imagination. "It is the special province of the medical schools and universities to foster medical research in this way," said Bush.

In addition to providing a constant flow of new, young talent, the university historically has an additional characteristic which makes it a natural environment for research--a tradition of academic freedom which protects the

ability of the researcher to follow leads as he or she is drawn. This is a major responsibility of the institutions.

The academic health center has much to gain from its research component. The linking of research and teaching is valuable to both enterprises. Education is diminished if it does not expose students to committed scholars and researchers. Moreover, the research enterprise also gains, for students with fresh ideas can often stimulate their mentors in the exploration of new avenues. The health care component of the academic center and the research undertaking also provide mutual enhancement. Health care workers may be stimulated to apply, as appropriate, the latest research advances, and researchers and students alike, by virtue of their exposure to patients, may be motivated toward some unforeseen but fruitful pursuit.

On the Government side of the partnership, the Bush report laid down another principle, that is virtually sacrosanct: the Government should make grants that would allow complete independence and freedom for the scientist to determine the nature, scope and methodology. "Scientific progress," he said, "results from the free play of free intellects working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown."

The key instrument NIH has used to provide support for free inquiry is the research project grant--the investigator-initiated grant--a project proposed to the NIH by the individual scientist and approved through the NIH peer review system. This type of grant is the mainstay of the Nation's biomedical research scheme, for we believe it fosters creativity and excellence. Experience shows that some of the most exciting and important research findings emerge from a

flexible system that permits diversity and allows individual scientists the freedom to pursue scientific leads according to their own creative energies.

A major reason for our emphasis upon freedom and flexibility in scientific support, and for defense of an open system based upon the creative initiative of the individual scientist or research group, is that one cannot predict where a discovery will have its major clinical application. There are notable examples where major research findings emerged from an unexpected quarter--from scientists following leads and gaining advances which could never have been anticipated or planned beforehand. A recent example is the story of Lyme arthritis--a disease which causes acute bouts of arthritis and in some cases meningoencephalitis, cranial nerve palsies, and cardiac abnormalities. Rheumatologists and epidemiologists at Yale, supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), discovered the disease and postulated that it was associated with certain types of small ticks. But it was an entomologist working with the National Institute of Allergy and Infectious Diseases (NIAID) in our Rocky Mountain Laboratory in Hamilton, Montana, who linked a newly discovered type of bacteria, a spirochete carried by the tick vector, to Lyme arthritis. This progress could not have been made had not the challenge been taken up by an individual researcher with particular expertise plus the freedom to proceed. The discovery in Lyme arthritis is also a testimony to the benefits which can accrue when scientists from various disciplines (in this case epidemiology, immunology, and entomology) collaborate fully.

A second notable example is the story of the viral association in juvenile diabetes. Although the NIADDK supports much of the basic research relating to

the etiology of diabetes, the virus finding emerged from a small group of investigators working under the auspices of the National Institute of Dental Research (NIDR). The scientists, led by a virologist, produced the first direct evidence that viruses are capable of causing diabetes in human beings. In 1978, the NIDR scientists learned of a 10-year-old boy who had died following an influenza-like illness of three days' duration. The scientists were immediately interested in the case since the boy was diabetic and had suffered from diabetic ketoacidosis. Moreover, the signs observed at autopsy were reminiscent of those they had observed in mice infected with diabetes-causing viruses. Using techniques they had developed in studying mice, the scientists managed to isolate a virus similar to Coxsackie B4 from pancreatic cells. Then, strains of mice developed in the laboratory--some susceptible and some resistant to diabetes--were inoculated with the virus from the child's pancreas. Within a week, a high percentage of the susceptible mice had developed diabetes, giving strong evidence that the child's diabetes had indeed been induced by the virus.

As so often is true of creative research, these two discoveries have raised as many research questions as they have answered. But the examples serve to illustrate that biomedical research is still at a point where the creative ideas of individuals play a large role.

In an effort to encourage such "free enterprise" research, NIH has historically relied upon the investigator-initiated project grant as its primary mechanism for the support of biomedical research. During the fiscal year which ended September 30, the NIH budget supported more than 15,000 project grants. Almost exactly 50 percent of our $3.6 billion budget for 1982 was used to fund these

grants. The term of the average grant is somewhat more than three years, so that each year, between one fourth and one third of our grants are either new awards or competitive renewals of existing grants.

Thus, they are an important element in another guiding principle held by the NIH--the need to provide for opportunities for new investigators to gain access to research grants, that is, the absolute necessity for assuring that an adequate number of the finest and brightest young minds in the current and coming generations find careers in biomedical research. An adequate number of first class biomedical research scientists in the 1980's and 1990's can only be maintained if graduate schools and academic health centers are successful in nurturing the research career interests of the young people who come to them for training.

NIH has a role to play here as well, since it is important that such young people have a reasonable expectation that they will have opportunities to apply themselves to research studies in their fields of interest when their training is completed. It is obvious that ample funds for the support of project research are an incentive for young scientists to choose research as a career and to stay with it.

Another important concern of the NIH is the general balance between basic and clinical research. We look to the academic health center to play a major role in building and maintaining a balance of these equally essential components of the research fabric for the Nation. A great deal has been said and written about the values of basic and clinical knowledge. In their classic study of the key contributions to cardiovascular and heart disease, Comroe and Dripps[2]

found that 41 percent of the work they judged to be essential for later clinical advance was not clinically oriented at the time it was done. The scientists responsible for the key findings sought knowledge for the sake of knowledge, to satisfy their own insatiable curiosities about the mysteries of nature.

Others[3] have cited examples where clinical observations and perplexing events provided major stimuli for great advances in science in general: protein chemists owe much to the study of sickle cell hemoglobin; much knowledge about the structure of antibodies is based on study of the myeloma protein; and vitamin B12 was first isolated by assays on patients with pernicious anemia. In addition, clinical investigators have made many important contributions to the understanding of human disease mechanisms.

The problem, obviously, is not to select one or the other for support, but how much emphasis to give to basic research and how much to clinical research?

There is perhaps no better example of the importance of supporting a balance of basic and clinical research than the story of hepatitis B. This saga illustrates the importance of serendipity, and is illustrative of the roles in research to be played by government, industry, and the university. The recent announcement by the FDA of the licensing of a new virus vaccine to combat hepatitis B, a debilitating liver disease, was the culmination of many years of hard work, both clinical and basic. The discovery that revolutionized the study of hepatitis came from an entirely unexpected quarter. Baruch S. Blumberg, an immunologist with an interest in human genetics, in 1963 became intrigued when a peculiar substance in the blood from an Australian aborigine caught his attention. Initially he thought he had discovered an evolutionary marker in the

blood of a primative people. Then he recognized that the substance might be a protein fragment left by an earlier infection. He doggedly followed up on the lead and within three years it brought him to the discovery of the hepatitis B virus. This work, which started as a basic inquiry, has led to many different lines of research, to a number of major clinical advances, and to the ultimate development of the vaccine. Along the way, Blumberg won a Nobel Prize. In his Nobel address he said, "At the outset we had no set views on where this path might lead--I could not have planned the investigation at its beginning to find the cause of hepatitis B." But between Blumberg's early discovery and the development of the vaccine lay a whole range of research studies, basic and clinical.

Our efforts over the years to protect the support of basic research have been remarkably successful, even in the face of continued and understandable public requests for attention to the urgent problems of today. As noted earlier, the support of basic research by the Government is now a national policy. George Keyworth[4] in a recent speech emphasized, "Basic research warrants government support because it is an investment in the future--in a better quality of life, better security, a better economy, and simply better understanding."

If the state of basic research is now secure, I still am concerned about an issue I wrote about in 1979[5]: "the clinical investigator as an endangered species"--the apparent long-term declining interest in biomedical research on the part of medical students, house officers, postdoctoral M.D. fellows, and young faculty.

There has been a steady drop in the number of M.D.'s serving as principal investigators on NIH investigator-initiated grants, and a concomitant decline in the success rate of M.D.'s who apply for NIH research grants. A recent NIH examination of the problem indicates that the lack of success has nothing to do with qualifications of the applicants, rather with flaws in research design as seen by the peer reviewers. This point brings me to the heart of my concern about training grants. From our studies of NIH grant holders, we know that applicants for investigator-initiated grants fare better in the peer review system if they have previously apprenticed under an NIH training grant. In a way, this fact is reason for optimism--it indicates that those trained have learned something about research project design and execution. But, it also heightens my concern about M.D. researchers since there has been a rather steady decline in the number of M.D.'s applying for NIH training grants as well as research grants. This, in my view, does not bode well for the future of M.D. principal investigators.

The reasons suggested for the decline in M.D. applicants for training are many. Whatever the reasons, it is my feeling that if we do not address this issue we may be missing out on important contributions to science and important advances in medicine. The matter is very complex, and needs to be addressed by NIH and the institutions.

My comments should not be taken as a disincentive to young investigators. There is a bright future in science for the clinical M.D. investigator who is adequately prepared, who has secured substantial training in science and in research methodologies. It is important to note, especially for the uncommitted student, resident or fellow, that although fewer M.D.'s are applying for

training grants, the success rate for those who do apply remains as high as in the past and it equals that of Ph.D. applicants.

The physician scientist has a very special role both in identifying relevant medical questions and in applying new knowledge to the investigation of disease. These roles cannot adequately be filled by Ph.D. scientists, however seminal and essential their contributions may be. The future of clinical science depends upon the quality and the number of new research leaders in the field. The quality is unquestionably there; potentially, so are the numbers.

It would be impossible to address the subject of "trends in NIH support for research" without taking some time to talk about the current budget situation for NIH and what this means to its partners in research.

When the funding for available project grants levels off--and, at the same time, the size of the average grant continues to grow--adjustments need to be made. The most vulnerable segment of our research support portfolio--new and competing grants--absorbs the shock. Other funding mechanisms, such as previously awarded grants, contracts and center grants, are less vulnerable because we are responsible for funding existing commitments before new awards are made.

To avoid closing the portal to the NIH project grant program--the very program we view as the centerpiece of the scientific undertaking--we have appealed to the administration and the Congress to help us maintain a relatively stable number of new and competing grants from year to year.

Although the general stringency of the budget has kept us from maintaining the level of 5000 new and competing grants--a level some consider to be a minimum--we hope that the stabilization effort will send a clear message to the young investigator that even in a time of constrained budgets, research support from the NIH is not restricted to the very few. Since more than half of our new project grants each year are made to first time principal investigators upon whom future productivity of the research enterprise rests heavily, it is not only prudent, but it is also essential, that this door be kept open.

We are aware that our efforts to stabilize research project grants within the constrained 1983 budget can bring on undesireable side effects complicating and possibly clouding NIH's relationships with its partners in research. Not the least of these side effects is the 10 percent reduction in payment of indirect costs.

It is not our intent, however, that this 10 percent reduction be a permanent measure, nor do we have any doubt about the fact that indirect costs of research are real. But they have been growing faster than direct costs and faster than inflation. We, as partners, need to consider how this growth can be controlled. Other issues are also on the agenda for the 1980's; the so-called "sliding scale" proposal which would spread NIH support for project research over a larger number of investigators. What might this mean to our committment to seeing that the very best research projects are adequately funded? As John Gardner[6] asked, "Can we be equal and excellent too?" Industrial-university collaborations in research. What effect might these arrangements have upon patents, the free dissemination of information and faculty loyalty? Peer review. Are changes necessary in the system to ensure that we support excellent

and innovative projects? Obsolescence of instrumentation. How can NIH contribute to the upgrading of necessary scientific equipment for use by its grantee institutions? And grant support for the salaries of tenured faculty. How does this practice affect relationships within the institution and what would be the consequences of alternative strategies?

In that now famous 1945 report, Vannevar Bush seems to have foreseen the potential strains in our partnership that can grow out of such issues, especially at a time when we will be required to adjust and readjust to financial uncertainty. The quite prolonged and truly splendid period of growth of the financial base for biomedical research is over, Government and universities alike must settle down and take a hard look at themselves and at each other.

But there is no need for pessimism. Together, the American academic institutions and the Federal Government have been responsible for creation of a research enterprise in the biomedical sciences whose benefits for the Nation are great. The prospects for the 1980's are bright. There is no reason to believe that the Federal/academic partnership, so well-founded, cannot respond to the challenges that may be presented in the next decade.

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[1]Vannevar Bush, Science--The Endless Frontier, 1945, Report to the President on a Program for Postwar Scientific Research.

[2]Julius H. Comroe, Jr. and Robert D. Dripps, "Scientific Basis for the Support of Biomedical Science," Science, Vol. 192, pp. 105-111, April 1976

[3]Arthur Kornberg, M.D., "The Lifeline of Medicine", New England Journal of Medicine, May 27, 1976, Vol. 294, pp. 1212-1216.

[4]Statement of Dr. George A. Keyworth, II, Director, Office of Science and Technology Policy, Executive Office of the President, before the Committee on Science and Technology, U.S. House of Representatives, December 10, 1981

[5]James B. Wyngaarden, M.D., "The Clinical Investigator as an Endangered Species," New England Journal of Medicine, December 6, 1979, Vol. 301, No. 23, pp. 1254-1259.

[6]John W. Gardner, Excellence: Can We be Equal and Excellent Too? Harper and Row Publishers, New York and Evanston, 1961.

Remarks*

NATIONAL HEALTH POLICY FORUM

by

James B. Wyngaarden, M.D.**

Three weeks ago, the National Heart, Lung, and Blood Institute announced the results of the Multiple Risk Factor Intervention Trial. This major study, involving 13,000 middle-aged males, was initiated ten years ago to evaluate the effect of the reduction of three risk factors in lowering the number of deaths from coronary heart disease.

The trial showed that lowering cholesterol, reducing high blood pressure, and quitting cigarettes do, in fact, make a difference.

But the study uncovered something else--a factor not fully appreciated at the time the trial was planned. One of the most significant findings came from the control group--the men who were given no special treatment. The study's risk-reduction interventions were not applied to them; they were given no specific recommendations and, according to the study plan, were expected to continue their customary patterns of medical care.

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*National Health Policy Forum
Ramada Renaissance Hotel, Washington, D.C.
October 7, 1982

**Director, National Institutes of Health

The study revealed that as a whole the members of the control group lowered their blood pressure and cholesterol levels--though not as much as the group receiving special treatment--and that they substantially reduced cigarette smoking.

These positive actions on the part of the normal care or control group were something of a surprise as was the more important fact that the mortality rate among the members of the control group was reduced below the expected level.

This happy development in the control group also caused the results of the special interventions to be less tidy than expected.

Even though the statistical demonstration of the value of risk factor reduction was blunted a bit, the trial illustrates in a dramatic way the state of change in American attitudes and actions with regard to health.

The somewhat unexpected results of the Risk Factor Trial bring to mind a recent article by my longtime friend--my predecessor as NIH Director, Don Fredrickson. Dr. Fredrickson, in writing about the whole of biomedical research, titled his paper with the rhetorical question, "Is Venice Sinking?" and answered it by saying, "No--The Water is Rising!"

Applying this typical Fredricksonian figure to the Risk Factor Trial, one could equate the rising water to the rising level of public response to good health practices. And this positive development is in turn the result of a rising level of knowledge about disease and health--the fruit of research.

This example also illustrates with force a major theme of this conference--the need to recognize and adjust to sweeping changes of many kinds in planning for health care in the years ahead. It is also a reminder to the scientific and health care communities that we are not the only game in town--that probably the most powerful intervention for good health can be made by members of the public out of concern for their own health.

For a few minutes I would like to discuss the role of biomedical research in bringing about more such changes--which are sure to come. While I doubt that any of us is wise enough to predict with much specificity the form and impact of such changes, it is clear that there are many areas of bright promise which, when fully exploited, can alter the patterns of medical practice and the costs of health care as profoundly as the emergence of antibiotics and the polio vaccine.

As an aside, let me point out that the discovery of antibiotics and their widespread use during World War II became a compelling argument for federal support of basic and applied biomedical research after the war. It was a most convincing demonstration of the value to the Nation of the fruits of biomedical research--a foretaste that convinced the policy makers of the time that substantial federal sponsorship of such research was an essential and appropriate function of government.

And in the years since the mid forties, the wisdom of those decisions has been confirmed and reconfirmed as new generations of policy makers have insisted

that federal expenditures for biomedical research represent a prudent investment of public funds. Just to state the amount of the current budget of the National Institutes of Health--$3.95 billion under the Continuing Resolution--is a way of summarizing the policy decisions affecting federal support of biomedical research since World War II.

In the State of the Union message this year--along with admonitions that the federal budget must be restrained--the President advocated an increase for the NIH of $108 million for research.

Perhaps it would be useful to discuss for a moment the discoveries that will change the practice of medicine in the 1980s. I will mention only a few:

The development of recombinant DNA technology gives us an exciting tool with which we can transfer hereditary units from one species to another. It permits, for example, bacteria to become "factories" that produce substances of biological, agricultural and medical importance. This technique has already led to the synthetic production of human insulin, somatostatin and growth hormone. These substances are now being tested in NIH-sponsored clinical trials to determine their effectiveness in treating insulin-dependent diabetes and certain types of dwarfism. Recombinant DNA technology also can be used to produce large quantities of pure antigen which, in turn, can be used as vaccines for immunization against infectious agents.

In addition, large quantities of highly specific antibodies can now be produced in the laboratory through the new technology of cell fusion and production of hybridomas. This process results in monoclonal antibodies which can be used to develop specific vaccines, diagnostic tests and treatments for many diseases. Recently, for example, investigators have used human lung cancer cells to prepare monoclonal antibodies which can distinguish human tumor cells from normal cells. This technology might permit the detection of cancer at a very early stage. Already there are limited examples of clinicians attaching radioactive or chemotherapeutic agents to the antibodies and, thereby, killing cancer cells without harming surrounding healthy tissue.

Remarkable progress has been made in understanding the immune system. Scientists have discovered genetic mechanisms that control the immune response to such invaders as cancer cells, transplanted organs and environmental substances that cause allergies. The genes that regulate these immune responses are called the major histocompatibility complex (MHC). Knowledge of clinical association between MHC and juvenile-onset diabetes, certain kinds of arthritis, Alzheimer's disease, chronic hepatitis, myasthenia gravis and other diseases provide tantalizing clues that may lead to better strategies to supplement natural resistance to these diseases and better techniques for organ and tissue transplantation.

An especially fruitful and expanding area of research is the neurosciences. This field is poised for existing developments in this decade. Investigators find more and more substances that have profound effects on the nervous

system--endogenous neurotransmitters and neurohormones, and well as many externally applied pharmacological substances. They act at "receptor sites" in many locations within brain or nerve tissue. An exciting area in neurobiology is the study of the body's natural painkillers--the endorphins and other opiate-like substances--which will provide fuller understanding of the mechanisms of brain function, the cause of substance abuse or drug addiction., and the treatment of pain. Their discovery has opened a whole new arena of research into psychoactive substances and their specific receptors in the body and brain. We are making steady progress toward the conquest of illnesses of the mind and body, such as depression, that have long baffled medical science. We are also beginning to understand the nerve regeneration in animals and tissue culture systems that may one day offer hope to victims of spinal cord injury.

Two new research instruments--the PETT Scanner (Positron Emission Trans-axial Tomography) and the NMR Scanner (Nuclear Magnetic Resonance)--are generally regarded as promising and versatile technologies that provide non-invasive methods for the study of organ structure, function and metabolism in living subjects. Like the CAT Scanner (Computer-Assisted Tomography), they promise to have a major impact on diagnostic medicine in the future.

However, the nature of research is such that any list of bright possibilities can prove an embarrassment--not so much because the promises may turn to disappointment, although that can happen, but mostly because something of tremendous importance may have been missed. Some minor finding that today

strikes an alert investigator as merely odd, can well trigger an unforeseen and totally new train of thought that leads to significant discovery. Remember that penicillin was first regarded as a mold that did strange things to cultures.

This prompts me to mention the rest of the penicillin story--the part in which American scientists played a critical role. The problem of production of the antibiotic in useful quantities was not an easy one--and until it was solved, the mold was only an interesting laboratory curiosity--though obviously a most promising one.

Development of research findings into applicable measures for diagnosis, prevention and treatment of disease is still a most challenging part of the research enterprise.

Similarly, once a new therapy or procedure is developed, it must be applied. While in the main the laws of economics and the pervasive dissemination of information on new therapies operate to bring the products of research and development into widespread use, there are exceptions; for example, the problems of the so-called "orphan drugs" for which there is little or no prospect of payback to industry for funds invested.

The NIH has taken an active role in technology transfer. For example, in 1977 the NIH established the Office for Medical Applications of Research as a focal point for special efforts to translate the results of biomedical research into the practice of medicine. One of the primary functions of that office is to coordinate Consensus Development Conferences on specific topics in medicine.

In this process, biomedical researchers, practicing health professionals, and others are brought together in a panel to exchange information and data on a specific health care intervention. The object is to seek and publicize to the professional community and the public as well the consensus of the panel on recommendations concerning the safety, efficacy and optimal use of new products and procedures.

The NIH's National Library of Medicine has a central role in the dissemination of research-derived information. It is the heart of a national and worldwide network offering researchers and medical practitioners the information they need in carrying out their essential functions.

Another important element of technology transfer is clinical trials. The NIH has sponsored a number of large trials aimed at improving the prevention and treatment of heart disease, hypertension, and diabetes. The expense of this vital activity, nearly $200 million annually in recent years, is one of our financial concerns which we must balance against the need to support investigator-initiated research.

We cannot disregard the fact that before there can be development of a new product or procedure, or a clinical trial, or transfer of a new therapy to the bedside, there must have been an initial exploration at the basic level.

The support of fundamental research is a means for actually creating a national resource and, in developing our budgets for the NIH, we assign the highest priority to funding of investigator-initiated research projects. In my confirmation hearing last Spring for the position of Director, I told the Senate panel of my commitment to the pursuit of basic research as the foundation for the understanding, treatment, and prevention of disease and disability, and of my belief that investigator-initiated research holds the greatest promise for significant discoveries.

At the same time I reminded them of a cautionary statement by Dr. Lewis Thomas that I feel should be a point of reference for this conference as consideration is given to the future of medical care.

Dr. Thomas, in an article that appeared in the New England Journal last year, said:

"We are beginning to draw from a bank of stored information in biomedical science and I suspect that we are doing something like this in the physical sciences as well. There is some danger that the need to continue depositing new information in that bank will be overlooked in the pressure for new applications . . . if things go on in this way, the country's basic science effort will come to a standstill, and the bank will go empty."

My own view of the future is a bit more sanguine than the possibility suggested by Dr. Thomas that we could overdraw our bank of basic biological knowledge. However, one of my major goals will be to preserve the traditional emphasis of NIH on basic research as the bedrock upon which all of the rest of the program structure is built.

As a corollary to emphasis on investigator-initiated research, I also want to stress the continued necessity for support for research training, for both physician and Ph.D. research scientists. Clearly if we are to have excellence and continuity in research, we must train scientists to carry on this work in the future.

At this point I would be glad to discuss further any of the matters I have touched on--or to hear your ideas or comments on the relationship of research to the future of medical care.

HEALTH POLICY TASK FORCE OF WOMEN IN GOVERNMENTAL RELATIONS*

by

James B. Wyngaarden, M.D.**

Within the past few months, I have had the opportunity to speak to a number of different groups about biomedical research, its future, and the role of the National Institutes of Health in that future. In most cases, the individual groups have been made up of persons interested in a particular facet of the research endeavor, either in an organizational sense or from the point of view of a specific disease category. For example, I have spoken to the American Lung Association, the American Psychological Association, the Association of Academic Health Centers, and the National Committee for Research in Neurological and Communicative Diseases, not to mention various committees of the Congress. None of the groups with which I have met has had as great a diversity of interests within the health field as is represented by your membership. So I consider this to be an unusual opportunity.

Mary McGrane suggested that I discuss the mission of the NIH, its current "condition," and what I believe the future will bring. That's a fair-sized order--but I will sketch in the background as best I can and hope that what I have to say will stimulate your questions about topics of special interest to you.

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*Breakfast Address before the Women in Government, AAMC.
Cosmos Club, Washington, D. C.
October 8, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

Perhaps the simplest statement of our mission is a one-sentence declaration that appears on the first page of the NIH ALMANAC. After identifying NIH as the Federal focal point for health research, the statement goes on to say, "Its mission is to uncover new knowledge that will lead to better health for everyone."

Our programs for basic research, developmental research, clinical trials, research training, and biomedical communications are considered as means for carrying out the assigned task, and each is essential to the success of that effort.

The unifying purpose is simple, but the organization which has been developed to carry out that purpose is not.

The NIH had its beginning nearly a hundred years ago in which was called "The Bacteriological Laboratory" at the Marine Hospital, Staten Island, New York. The name was soon changed to The Hygienic Laboratory. The stated purpose of the laboratory was "for research on cholera and other infectious diseases." Gradually, in the intervening years, the mission was expanded by the scientists working in the laboratory to include research on health problems other than communicable diseases.

The first isolated skirmish in the war on cancer occurred in 1927 when Senator Matthew Neely of West Virginia introduced a bill authorizing a five million dollar award for a "practical and successful cure for cancer." The bill didn't move. A year later, Senator Neely was defeated. But his interest must have had some effect for in 1934 a President's panel, when asked to recommend topics for increased Federal health research, listed cancer first, followed by heart disease, tuberculosis, malaria, venereal disease, and dental problems. Though not considered a mission statement for the Federal laboratory, this recommendation was a step in the evolution of the present global mission of the NIH.

As a newcomer to NIH administration, I can say without appearing to boast that the structure that has evolved to carry out the organization's mission is unique and truly remarkable. During the past months as I have given intensive study to the operations and operating philosophy of the NIH, I have come to appreciate in a new way the vision and good judgment exercised by policy makers at critical times in the development of the Agency as an instrument for carrying out its important mission.

We tend to forget that the investment of any substantial amount of Federal funds in biomedical research did not begin until the 1940s. Incidentally, that was more than 50 years after agricultural research was accepted as a Federal responsibility.

But until the United States entered World War II, most biomedical research in this country was conducted in medical schools and universities under the sponsorship of private foundations or paid for by the institutions themselves.

This dependence on private philanthropy stands out clearly in the title of the Congressional enactment that changed the name of the old Hygienic Laboratory to the National Institute of Health. The 1930 Law known as the Ransdell Act, so named for its author, Senator Jonathan Ransdell, was entitled "an Act to establish and operate a National Institute of Health, to create a system of fellowships in said institute, and to authorize the Government to accept donations for use in ascertaining the cause, prevention, and cure of disease affecting human beings, and for other purposes."

In a statement at the introduction of the bill, Senator Ransdell described the Federal role he envisioned saying that the Government . . . "should show no rivalry or jealousy toward private endowments, foundations, institutions, schools, municipal and state health departments, but merely a friendly leadership in a concentrated effort to conquer disease and relieve human suffering, to prolong the term of life, and make our sojourn on earth more pleasant and free from pain . . ."

"Philanthropists may well be encouraged to establish endowments for the conduct of research and above all for the training and employment of scientists. They may be encouraged also to make donations for the use of the Federal Government in the promotion of scientific effort."

The Senator concluded his plea for the bill by observing, "I cannot suggest anything . . . that will do so much good to humanity as to contribute generously to their Federal Government for public health purposes in combating disease."

However, it was the realization of wartime needs that brought the Federal Government into biomedical research on a significant scale for the first time. Not only was the decision made to accept the conduct and support of such research as an important function of Government, it was also decided that such activities would be carried out in partnership with the the private and public institutions which had been mobilized as a part of the war effort.

Forty years later, as we enter the fifth decade of the Federal-academic partnership in biomedical research, one can take courage about making at least some predictions about the 1980s from the fact that the basic principles shaping that partnership have changed very little since the years immediately after World War II.

The Ransdell view of the NIH as a more or less passive coordinator--the "friendly leader . . . showing no jealousy toward private endowments"--doesn't describe the NIH of today, though I would hope that we are a friendly leader. Further, one of our current concerns is to find our most useful role in a three-way partnership involving government, academia, and industry. As you know, some of our largest academic institutions are beginning to receive substantial support from industry for conducting biomedical research under a variety of organizational arrangements.

The Federal Government, however, continues to support about 60 percent of biomedical research in this country--the NIH alone conducts or supports 40 percent of it.

The natural, or as I see it, the inescapable role of government is the support of fundamental or basic research. George Keyworth, the President's science advisor, expressed clearly this Administration's view of the Federal function in research. In a statement last December, he said, "Let me emphasize again that this Administration views basic research as a vital investment with a good return and believes that as a contribution to overall national security and economic strength, we must maintain health across the spectrum of science, striving for excellence in all these fields."

He, of course, was speaking of science in general, but his statement applies fully to biomedical science. He added, "Arguments for a government role in civilian research and development apply most strongly to basic research" and noted that "While some basic research is supported by the private sector, the results of basic research do not generally show up directly as new products or production processes, but as information and knowledge that are easily and widely available to everyone. Thus, there is less incentive for firms to support basic research."

Longtime NIH watchers have told me that President Reagan's mention of the Agency in his "State of the Union" message early this year was highly unusual--his request at that time for an additional $108 million for biomedical research stood out in contrast against his general appeal for the curtailment of Federal expenditures.

This is not to say that we have no financial problems. The development of the 1983 budget involved some difficult choices--and some of the necessary adjustments haven't been greeted with enthusiasm in all elements of the scientific community.

The NIH budget for 1983 is not settled and pending further action when the Congress returns late next month, it is difficult to be very specific about our programs for the coming year. Our priorities, however, are clearly expressed in the original budget request.

For example, nearly half (or 49.5 percent to be exact) of our request is for funds to support investigator-initiated research projects. We consider such projects to be the bedrock on which our programs of research are built. These projects represent the original thinking of some of the finest, most experienced investigators in academic institutions throughout the Nation.

Not only do investigator-initiated projects give access to an unlimited horizon of ideas--this program serves another and equally important purpose. It is through the research project grants that many of our young investigators enter the productive phase of their research careers. The term of the average grant is something over three years, so each year between one-fourth and one-third of our roughly 16,000 grants are either new awards or competitive renewals of existing grants. Within a given budget, the amount of funds available in any year for new and competing grants is affected by the awards made in the immediately preceding years--our continuing commitments--and the number of new and competing awards depends also upon the average size of such grants.

We have made a special effort to assure that a predictable and substantial number of new and competing grants can be made each year. The future productivity of the research enterprise depends heavily upon the input of ideas represented by the new proposals--and just as heavily on the newcomers who are supported to carry out the proposed studies. About 12 percent of all our grant projects at this time are being carried out under principal investigators who are supervising their first NIH-supported project. Half of our new project grants each year are made to first-time applicants.

In addition to our deep interest in assuring a continuing renewal of the body of first-class scientists willing and able to pursue creative careers in biomedical research, we feel a special obligation to assure that the investment

of public funds is made responsibly and prudently. Four-fifths of our budget is used for the support of research outside our own agency in universities, teaching hospitals, and research institutes. Many of you are familiar with the mechanisms used by the NIH in assessing the quality of proposals. I'll be glad to discuss the peer review system further if you wish.

During the coming year, we expect to be able to make awards to only about 30 percent of the applicants whose proposals are considered eligible for support. Scientists and administrators from academic and other research institutions have noted that competition for funds from the NIH and other sponsors is intensifying year by year and shows no signs of abating. They make the point that never before have so many established investigators faced so much uncertainty about their future as active scientists, and never before have so many novices faced so many disincentives to entering or continuing a research career.

Suggestions have been made of various methods for spreading NIH funds over a greater number of grantees by use of a sliding scale of progressively decreasing support, keying the amounts awarded to the technical merit ratings assigned to applications. Such a practice would represent a departure from the criteria that have constituted NIH policy for several decades, including scientific merit and program relevance.

John Gardner said it better when he asked, "Can we be equal and excellent, too?"

I would like now to touch briefly on the third topic that Mary McGrane suggested--my belief about what the future will bring. Rather than speculate about budgets and mechanisms of support, I would like to mention a few areas of scientific promise--the kinds of things research is all about.

For example; the development of recombinant DNA technology, an exciting tool which permits us to transfer hereditary units from one species to another. It makes it possible to use bacteria as "factories" for the production of valuable substances of biological, agricultural, and medical importance. This technique has already led to the synthetic production of human insulin, interferon, and growth hormone.

These substances heretofore have been available only by extraction from animal and human tissues and some, like growth hormone and interferon, have been extremely expensive. Recombinant DNA-produced forms of these substances are now being tested in NIH-sponsored clinical trials to determine their effectiveness in treating insulin-dependent diabetes, certain types of dwarfism, and in the case of interferon, its effectiveness in treating types of cancer. Recombinant DNA technology also can be used to produce large quantities of pure antigen which in turn can be used for immunization.

Another area of promise is in the use of cell fusion to create hybridomas for the production of highly specific antibodies to be used for specific vaccines, extremely sensitive diagnostic tests, and for treatment of many diseases. This technology may permit the detection of cancer at a very early stage and eventually the antibodies may be used to carry radioactive or chemotherapeutic agents to kill cancer cells without harming healthy tissue.

Remarkable progress is being made in understanding the immune system. Scientists have discovered genetic mechanisms that control the immune response to such invaders as cancer cells, transplanted organs, and environmental substances that cause allergies. The knowledge to be gained may lead to better strategies to supplement natural resistance in warding off juvenile-onset diabetes, certain kinds of arthritis, Alzheimer's disease, and chronic hepatitis, and to the development of better techniques for organ and tissue transplantation.

An especially exciting and expanding area is research in neurobiology. Investigators are finding more and more substances that have profound effects on the nervous system. One fruitful area is the study of the body's natural pain-killers--the endorphins and opiate-like substances--from which we hope to gain a fuller understanding of the mechanisms of brain function, drug addiction, and the treatment of pain.

New instruments have been developed--the PETT Scanner (Positron Emission Transaxial Tomography) and the NMR Scanner (Nuclear Magnetic Resonance)--which provide noninvasive methods for the study of organ structure, function, and metabolism in living subjects.

These advances represent only a few of the many recent achievements which are the outgrowth of the revolution in biomedical research. Today, a major challenge facing the NIH and the scientific community as a whole is to build on those advances, to maintain the capacity of the national biomedical research enterprise, and to sustain momentum in the face of fiscal restraints.

I would be pleased to hear your comments and to attempt to answer any questions you may have.

REMARKS FOR MEETING WITH NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL

October 12, 1982

I am delighted to have this opportunity to meet with the National Advisory Research Council at this time--and particularly for two reasons.

First, I wish to express personally and on behalf of the NIH community our sincere appreciation to Jim O'Donnell for his able and dedicated service as Acting Director of DRR for an extended period - from January 1981 until the first of October of this year. To serve in an acting capacity so long and so well is not an easy task and requires unusual devotion to our common goals. For this, Jim, - our special thanks.

I am also pleased to be present at the first meeting of the Council since Betty Pickett's appointment as Director.

She, too, has had the experience of presiding as an Acting Director, having served from July in 1981 until July 1982 in that capacity at the National Institute of Child Health and Human Development. You know of her distinguished career in the National Institute of Mental Health, the National Institute on Aging, and the Child Health Institute. We are fortunate, indeed, to have found a person with Dr. Pickett's varied experience and qualities of leadership within our own organization -- I commend her wholeheartedly to you.

FIRST DEWITT STETTEN, JR., LECTURE AND THE TWENTIETH ANNIVERSARY OF NIGMS*

James B. Wyngaarden, M.D.**

Thank you Dr. Kirschstein.

Dr. Stetten; distinguished guests:

Tonight we commemorate the 20th anniversary of the National Institute of General Medical Sciences, aptly marked by a masterful lecture on basic genetic research by Dr. Hogness.

In reflecting on the origin of NIGMS in 1962--or really 1958, when its predecessor Division was formed--I tried to recall the more significant events of that period.

They were exciting and rewarding days in the new Clinical Center. As Bob Cohen said in the chapter he wrote for Hans Stetten's history of the intramural program: "It was good to be young in a young institution."

Origin of the Institute in Context

But other events of those years had a more global import. Consider what was happening in the NIH programs:

Marion Folsom, a Secretary of HEW under Eisenhower, had stated as a policy that no worthy NIH grant application should have to be turned down for lack of funds.

Congress agreed, and the NIH appropriation went from $98 million in 1956 to $213 million the following year--a 117 percent increase and a unique event in NIH history.

In June 1958 a group of consultants to the Secretary, chaired by Stanhope Bayne-Jones, issued a report on medical science and education. It recommended wider support of the Nation's research and research training through expanded NIH programs.

Administrative machinery already running led to the creation of DGMS the following month, with programs acquired from DRG and a budget of about $15 million.

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*Lecture presented in Terrace Room, Naval Medical Center on October 13, 1982.

**Director, National Institutes of Health, Bethesda, Maryland 20205.

Four years later, NIGMS was established with a budget at the $100-million level. The program had already grown 6- or 7-fold. The Institute received its first direct appropriation from Congress in 1966 for $127 million.*

Thus the new Institute was a major factor in the general expansion of NIH. The establishment of effective new programs was challenging, and well executed, at that time.

Mission

The mission of NIGMS is stated in Public Law 87-838. The Surgeon General was to establish an Institute for the conduct and support of research and research training in the "general or basic medical sciences and related natural or behavioral sciences." These activities must have significance for two or more other Institutes of NIH or be outside the other Institutes' areas of responsibility.

NIGMS today has certain "earmarked" functions, such as administration of NRSA, the MARC [Minority Access to Research Careers] program, trauma-burn research, and specialized research centers.

But the spirit of the authorizing legislation is strongly manifest in the Institute's research programs and policies. Basic research continues to be its main thrust. This has proved a most fruitful approach to medical progress.

Productivity of Basic Research

During Dr. Stetten's administration of the Institute between 1970 and '74, NIGMS research support was organized into five main programs: Cellular and Molecular Basis of Disease, Genetics, Pharmacology-Toxicology, Clinical and Physiological Sciences, and Biomedical Engineering.

True to the spirit of the Institute's basic science mission, this was the limit of its effort to "program the unknown." R&D contracts, even in those years of heavy "targeting," never exceeded 3 percent of the budget. (In 1981 they were 0.2 percent.)

Yet the Institute's research projects--supported almost entirely by investigator-initiated awards--are consistently productive of important new knowledge. This is indicated, for example, by the success of the Institute's grantees in winning Nobel prizes. Of the 59 Nobelists NIH supported before their selection as laureates, 31 had received grants from NIGMS (or DRG).

A similar index of payoff is the frequent citation of NIGMS-supported research papers in 275 selected journals.

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*Formerly funded from General Research & Services appropriation.

Dedication

We are here not only to commemorate the 20th anniversary of a most successful and productive institution, but also to honor Dr. Stetten, its third Director.*

Since leaving that office, Dr. Stetten has held several distinguished positions, both at NIH and as the first dean of Rutgers Medical School.

A scientists' scientist, he has always been regarded by his colleagues with great admiration and deep affection. And he has left the mark of his wisdom, integrity and humanity wherever he has served. I can think of no one to whom a lectureship in the biomedical sciences could be more aptly dedicated than DeWitt Stetten, and I am delighted to have been asked to introduce him this evening.

Thank you.

*Not counting Dr. G. Halsey Hunt, Director of DGMS. Early Directors of NIGMS were Drs. Clinton C. Powell and Frederick L. Stone.

WAKEMAN AWARD SYMPOSIUM*

Remarks

By

James B. Wyngaarden, M.D.**

Part I--Introduction to Wakeman Symposium

I am very happy to be back here at Duke for the sixth Wakeman Award Symposium, and the third Division of Neurology's. I consider it a great honor, Dr. Roses, to chair the symposium.

This Wakeman Symposium serves as a powerful reminder to me, for it is also a prototype of what the NIH is all about. The NIH mandate, in one of its simpler forms, is to foster--in a partnership with academic institutions--an environment that encourages creativity and excellence in biomedical research. Experience shows that some of the most exciting and important research findings emerge when individual scientists (or research groups) are free to pursue scientific leads according to their own creative energies.

Emphasis on basic research is important in all scientific fields, but this emphasis has special significance in the neurosciences--a field which is really still in its infancy--as measured by the vast array of unknowns remaining. And,

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*Duke University, Durham, North Carolina, October 15, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

if the neurosciences are on the frontiers of biomedical research, then our speakers today are the vanguard in their specialized area of basic research.

When I was a medical student, no one considered investigations into nervous system regeneration. That was simply an impossibility. Even just a decade ago, few scientists were investigating the complex mysteries of nerve regeneration. Spinal cord injury was recognized as a problem of utmost importance to society as reckoned by the fact that some 200,000 Americans are confined to wheelchairs because of spinal cord injury, with 10,000 new injuries each year. But, for the most part, attention was placed on learning how to provide better acute care and on developing prostheses to help those injured to manage with their inevitable handicaps.

Few scientists were stimulated to pursue basic studies in nervous system regeneration--perhaps it seemed too hopeless an area. Some scattered work was done, but in general, enthusiasms waned each time these limited efforts failed to fulfill initial expectations. What was needed was a more solid base of fundamental knowledge.

This unpromising situation began to turn around about five years ago when the NINCDS--the principal NIH component supporting neurological research--began a major new initiative to stimulate basic inquiries relating to nerve regeneration. Skeptical neuroscientists began to see that there was, indeed, reason for them to turn their energies to this area. Valid scientific clues to understanding neuronal regeneration had been gained. And methods did exist that could be employed to expand the knowledge base.

Fundamental knowledge acquired by our three speakers and others who entered the field, gradually accumulated to the extent that by 1980, basic research in nervous system regeneration had doubled in just about five years. Several state-of-the-art conferences were held at about this same time from which participants emerged confident that they could identify nervous system regeneration as a reasonable research target for the future.

That promise of the future still lies ahead of us, but we look forward to it with a good deal more optimism now.

Our three speakers today are the originators of some of the most important and seminal information we now hold about this complex and fascinating field of research. There is no doubt that their work will form the basis of much research yet to come, that they will serve as role models for new investigators in the field, and that their work will eventually contribute to improved management of patients with spinal cord injuries.

Our first speaker is Professor Silvio Varon.....

Part II--For the Evening Presentation of the Award

The importance of research in the neurosciences is incontestable. Approximately a million Americans suffer from neuromuscular diseases, more than a million elderly have senile dementia, close to two million are disabled by stroke, and between two and four million people have epilepsy. Two hundred thousand more are paraplegics. It is impossible to estimate the costs of neurological disorders in dollars or in terms of human suffering. Moreover, the neurological disorders are some of the most perplexing disorders that afflict mankind--for example, amyotrophic lateral sclerosis, Huntington's disease, and the bacterial and viral infections of the nervous system. Some of these disorders are curable today. For many others, the only hope is research.

On the brighter side, the field of neuroscience is one of the most exciting areas of research today, partly because as a research endeavor it is still a relatively new field and because it is at a point where tools and methods are available for the accumulation of basic knowledge.

In the past 30 years, tremendous progress has been made in research on the nervous system, both in health and in disease.

In 1950, the light microscope was still the principal means of looking at a nerve cell, and could at best achieve a magnification of 1,000 diameters. Today, electron microscopes commonly give us three-dimensional views of nerve cell components, enlarged 50,000 times.

In 1950, staining techniques made it possible to distinguish one nerve cell and its processes from another, under the light microscope. Today, with positron emission tomography, or PET scanning, we can "watch" what happens to radioactively tagged natural substances, such as oxygen and glucose inside the living nerve cell deep within the human brain.

In 1950, neuropharmacology was essentially empirical; derived from trial and error. Today we have a substantial body of rational theory, and an increasing number of treatment procedures based on knowledge derived from research.

In 1950, there were only a few towering figures in the field of neurosciences, centered in a handful of the world's great universities. Today we have a community of about 6,000 senior investigators in the neurosciences.

The 30-year span I have been describing corresponds to the 30 years of major National commitment to neurological research. It was approximately 30 years ago that the National Institute of Neurological and Communicative Disorders and Stroke was established at the NIH.

And, though we have come this long way in 30 years, the neurosciences, as much as any area of research, still represent a frontier of biomedical science.

As John C. Eccles, has said[1], "I have observed the main developments in neurobiology and I have come to see that we are still in a stage where the imaginative ideas of individuals play a leading role. ....this situation arises

because so much that is unpredictable occurs in our scientific investigations. We must therefore cherish the flexibility that comes from personal control. Each experiment is an adventure into the unknown."

In one of its simplest forms, the mandate of the NIH and the NINCDS is to set policies--in partnership with academic institutions--to foster just the kind of atmosphere suggested by Eccles. Our joint mission is to provide the individual worker with an opportunity for free study of nature, in the directions and by the methods suggested by his or her interests, curiosity, and imagination.

Nowhere is the need for newly well-trained and enthusiastic young investigators more important than in the neurosciences. What draws able young people into a particular field is the demonstration that progress is being made, that the field is wide open to those of excellence, and that role models exist to emulate.

The symposium given by Drs. Varon, Bunge, and Aguayo this afternoon was one of the most exciting and encouraging series of presentations I have heard in a long time. There is still a long way to go in CNS regeneration but this work represents a giant stride forward. The Wakeman Award, its fine history, and particularly our 1982 Wakeman laureate serve to send a clear, strong message of hope to us all.

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[1]John C. Eccles, "The Discipline of Science with Special References to the Neurosciences," Daedalus, Spring 1973, pp. 85-99.

CFC KICKOFF*

Remarks

By

James B. Wyngaarden, M.D.**

AMERICANS STILL CHERISH THE CONCEPT, FOSTERED BY OUR HISTORY, THAT CONCERNED CITIZENS VOLUNTARILY WORKING TOGETHER CAN RESPOND SATISFACTORILY TO SOCIAL NEEDS. ALEXIS DE TOCQUEVILLE, THE INTREPID FRENCHMAN WHO IN THE EARLY 1800'S UNDERTOOK TO WRITE A MASTERPIECE, "DEMOCRACY IN AMERICA," MADE SOME OBSERVATIONS IN THIS REGARD AFTER HIS VERY FIRST, BRIEF VISIT TO THIS COUNTRY.

ONE OF THE TRAITS THAT STRUCK HIM IMMEDIATELY WAS THE PROCLIVITY OF THE AMERICAN PEOPLE, ON A COMMUNITY LEVEL, TO RESPOND TO THE DEMANDS FOR EDUCATION, ASSISTANCE FOR THE OLD AND NEEDY, AND CARE FOR THE SICK. AND ALWAYS, HE NOTED ON A VOLUNTARY BASIS.

HE SAID, "IN NO COUNTRY IN THE WORLD HAS THE PRINCIPLE OF ASSOCIATION BEEN MORE SUCCESSFULLY USED, OR APPLIED TO A GREATER MULTITUDE OF OBJECTS THAN IN AMERICA." BACK THEN, PHILANTHROPY WAS AN EMERGING FORM OF NEIGHBORLINESS.

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* National Institutes of Health, October 29, 1982

**Director, National Institutes of Health,
Bethesda, Maryland

AS IS OBVIOUS FROM THE NIH TRADITION OF RESPONSE TO THE CFC, WHAT THE FRENCHMAN OBSERVED STILL OBTAINS. THERE REMAINS SOME INTRINSIC QUALITY THAT MAKES US WANT TO CONTRIBUTE TO PERCEIVED COMMUNITY NEEDS.

BUT MANY PEOPLE WORKING IN THE WASHINGTON AREA, BECAUSE THEY HAVE MOVED HERE--AS I DID--FROM OTHER LOCATIONS, HAVE A TENDENCY TO FEEL THAT THEY DON'T LIVE HERE. THEY STILL THINK OF 'HOME' AS ELSEWHERE. WELL, THE WASHINGTON AREA IS OUR COMMUNITY, OUR HOME. AND WE DO HAVE A RESPONSIBILITY TO CONSIDER ITS NEEDS AND DECIDE HOW WE CAN BEST RESPOND.

THE CFC GIVES US AN OPPORTUNITY TO TAKE A PRIVATE APPROACH TO SOME PRIVATE PROBLEMS--AND TO CONTRIBUTE TO COMMUNITY PROJECTS SUCH AS YOUTH COUNSELING, AID FOR THE NEEDY, MEDICAL REHABILITATION, AND MANY, MANY MORE.

THE CFC IS A MASTERFUL ADMINISTRATIVE VEHICLE THAT PROVIDES EXPOSURE TO A MYRIAD OF CONCERNS--THERE ARE MORE THAN 250 ASSOCIATIONS FALLING UNDER CFC--EACH CONTRIBUTOR CAN MAKE A THOUGHTFUL DECISION ON WHICH ACTIVITIES TO SUPPORT.

THE CFC SYSTEM OF DESIGNATED GIFTS AND THE DEVICE OF PAYROLL DEDUCTION MAKES IT CONVENIENT AND FEASIBLE FOR US TO CONTRIBUTE IN AN ACTIVE, DECISIVE WAY.

PAYROLL DEDUCTION ALLOWS US TO HELP ALL YEAR LONG, AND THE DESIGNATION OF RECIPIENT GROUPS PERMITS US TO MAKE A VERY PERSONAL ALTRUISTIC STATEMENT.

I URGE YOU TO MAKE A CONTRIBUTION TO CFC THIS YEAR--YOUR CONTRIBUTION WILL BE TRANSLATED INTO HIGHLY PERSONAL TERMS FOR THE THOUSANDS UPON THOUSANDS OF INDIVIDUALS WHOSE LIVES ARE TOUCHED AND IMPROVED BY THE SERVICES OF THE VOLUNTARY AGENCIES SUPPORTED THROUGH CFC. WE KNOW OF THE GOOD WORK SUPPORTED BY THE CFC AND ARE COMMITTED TO ITS SUCCESS.

BIOMEDICAL SCIENCE POLICY AND CLINICAL RESEARCH*

By

Mortimer B. Lipsett, M.D.**

Dr. Wyngaarden wanted very much to be here today, because one of his keenest interests even before coming to NIH as Director, has been the state of clinical investigation in this country. He wanted to deliver a message to this group about NIH's concern and optimism regarding clinical research. I am grateful to have this opportunity for I share Dr. Wyngaarden's views about the importance of clinical research both to science and to medicine in the next decade.

Never in the history of clinical research has the pace of science been so swift. A well-conceived emphasis on maintaining a productive community of basic scientists has produced an ever-increasing store of fundamental knowledge. The findings in just the last 10 years in virology, molecular biology, pharmacology, cell biology and immunology greatly extend the opportunities for clinical investigators. Continuing the research on hybridomas, DNA recombinant technology, and oncogenes, for example, needs—for further advancement—the input of clinical investigators.

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*Opening Lecture at the Plenary Session,
Central Society for Clinical Research
Drake Hotel, Chicago, Illinois, November 5, 1982.

**Director, National Institute of Child Health and
Human Development, National Institutes of Health,
Bethesda, Maryland.

It is not necessary before this group to define clinical research. But, I would like to reiterate a theme stressed at a recent meeting by Dr. John Oates, of Vanderbilt.[1] To many, clinical research has become synonymous with the term "technology transfer"—conveying the impression that clinical research is, in a way, an applied art rather than a science. True, society owes a great debt to clinical trials of, for example, antimicrobials and cancer drugs. But that is a truncated definition. We must be sure, especially for the sake of our students, to make clear that clinical research is much more than "application." Clinical research is also discovery. It is an occupation that requires imagination and creativity coupled with an ability to conceive of a hypothesis, apply rigorous methodology, and execute painstakingly. To do this and involve and maintain close contact with the realities of clinical medicine is a towering challenge.

Some of the very best clinical research is recognized annually by the Lita Annenberg Hazen Award, to be announced for 1982 in just a few days. Past winners—Jesse Roth for explaining the basic defect in cell receptors in diabetes in the obese, Henry Kunkle for demonstrating the role of circulating immune complexes in disease, and Aaron Lerner for elucidating the biology of benign and malignant pigment cells—all exemplify the very best of clinical research. Their work surely serves to point up the discovery aspect of clinical research and its translation to the clinic.

This need to provide the environment that attracts such investigators will be the subject of much of my talk today and is a subject of great interest to Dr. Wyngaarden as the new Director of NIH.

Concern for the future of clinical research is the obligation of the NIH, this society, and the medical schools. It is up to us to portray the satisfaction that can come from clinical research as a career. For there are disincentives for young people in the throes of making career decisions. Further, many are drawn into careers in medical practice with the idea that they will contribute to improving health and saving lives. We need to let students know that in clinical research there is opportunity not only to have the rewards that accrue to the true physician, but also the chance to experience the excitement that comes from discovery.

C.P. Snow in his novel "The Search" describes this excitement:

> "Then I was carried beyond pleasure. My own triumph and delight and success were there but they seemed insignificant beside this tranquil ecstasy. It was as though I had looked for a truth outside myself, and finding it had become for a moment part of the truth I sought; as though all the world the atoms and the stars were wonderfully clear and close to me and I to them so that we were part of a lucidity more tremendous than any mystery.
>
> "I had never known that such a moment could exist."

That experience, described so beautifully, is one of the greatest rewards that clinical research can bring to the physician. It is the existential pleasure of science, the gratification that comes from the inmost depths of our being independent of medical theory, clinical science, or social need.

I believe that our own words and actions as clinical investigators are critical to the future of our profession. In his book "Excellence; Can We Be Equal and Excellent Too?",[2] John Gardner remarked that the influx of excellent new people into a given field in large part depends upon the morale of that field. And a major component of our collective morale is the optimism and encouragement that we can bring to newcomers and to those on the brink of decision.

We are not asking for a large number of medical students to choose clinical research over practice—perhaps only five to six percent of medical school graduates. But we need to count on the medical schools to help us find and nurture those few. There must be a way to assure that at least some of the students get some exposure to experimentation early in their studies with the hope that a few will become enchanted and continue to seek training opportunities throughout their pre- and postdoctoral work.

In a recent survey[3] of senior medical students by the AAMC, students who expressed an intention of choosing a research career selected as one of the three most important motivating factors "research experience while a premedical or medical student." (The other two factors were "opportunity to work in an academic community" and "challenge of search for new knowledge.")

It is my impression that it is the exposure to the research process, not exposure to a given field of research that is essential. Many, many investigators who went on to be recognized in a particular field did their first work in an entirely different area. For example, Carleton Gajdusek's first work was synthesizing a large series of halogenated aryloxyacetic acids (later put into commercial use as a weed killer). Dr. Aaron Lerner's first research interest as an undergraduate was in mathematics and the physical sciences. Later, working on fatty acids with Dr. George Burr, he became "hooked" (as he put it) on the biological sciences. Dr. Wyngaarden's first papers were on anesthetics, though he went on to be internationally recognized in the genetics of gout and the regulation of purine biosynthesis.

Apparently, what is needed is exposure to the research atmosphere, perhaps a good role model, and a taste of discovery and excitement, to fire up an aspiring clinical researcher to the point where he or she is willing to take the challenge.

However, our assurance to students about the excitement and fulfillment that can come from clinical research is not enough. The new or would-be investigator needs to know that there is a full career open to him or her in research. This is where the NIH plays a major role.

Historically, NIH has relied upon the investigator-initiated project grant as its primary mechanism for the support of biomedical and behavioral research. During this last fiscal year, the NIH budget supported more than 15,000 project

grants, and almost exactly 50 percent of our $3.6 billion budget for 1982 was used to fund these grants. The term of an average grant is somewhat more than three years, so that each year, between one-fourth and one-third of our grants are either new awards or competitive renewals of existing grants.

These investigator-initiated proposals are the raison d'etre for the NIH: but we must provide opportunities for new investigators to gain access to research grants—in fact it is an absolute necessity to ensure that some of our finest and brightest in the current and coming generations find careers in biomedical and behavioral research.

We know that an adequate number of first class biomedical and behavioral research scientists in the 1980's and 1990's can only be maintained if universities and medical schools are successful in nurturing the research career interests of the young people who come to them for training. Since it is important that such young people have a reasonable expectation that they will have opportunities to apply themselves to research studies in their fields of interest when their training is completed, it is obvious that ample support of project grants is an incentive for the young to choose research as a career and to stay with it.

Although the general stringency of the budget has kept us from maintaining the level of 5000 new and competing grants—a level some consider to be a minimum—we hope that the stabilization effort will send a clear message to the young investigator or the young person still considering a research career—that

even in a time of constrained budget, research support from the NIH is not restricted to the very few. Since more than half of our new project grants each year are made to first-time principal investigators upon whom the future productivity of the research enterprise rests heavily, it is not only prudent, but it is also essential, that this door be kept open.

Recently the scientific community has questioned Government's commitment to the training of new investigators. NIH has always accepted this as one of its major responsibilities. We estimate that the NIH now supports between 85-90 percent of all postdoctoral training in clinical research. A variety of mechanisms are available as you will see in the next two slides.

SLIDE 1 - Selected NRSA Awards

Authority for the training of biomedical investigators was first provided in 1930. By 1971, NIH training grants and fellowships supported or assisted 37.5 percent of the nation's full-time graduate students in the medical science and 21 percent in the life sciences. In 1973, the Administration proposed phasing out the research training grant and fellowship programs of the NIH, ADAMHA, and HRA. The Congress, however, passed the National Research Service Award Act of 1974 (Title I, Public Law 93-348) which abolished previous research training authorities under the PHS Act and consolidated them in a new mechanism called the National Research Service Award (NRSA). Under this new authority, the Secretary of HHS is directed to provide both predoctoral and postdoctoral support to individuals and additional support to institutions training such individuals.

The Institutional Training Grant. These awards are made to institutions on behalf of a program director who is responsible for the selection and appointment of both pre- and postdoctoral trainees and for the overall direction of the program. A new program under this type of grant is the Post-Sophomore Opportunity—advertised for the first time in August, and a special interest of the NIH Director. Its purpose is to offer students—during a time of intense decision making about career choices—the chance to interrupt their preclinical studies with some exposure to research prior to resuming their clinical education. It is during this decision-making period that exposure to research could capture the future Jesse Roths, Aaron Lerners, and Henry Kunkles. The program is open only to "professional students"—those in medical, veterinarian or dental schools.

The Individual Fellowship. This award is made for full-time postdoctoral research training for health scientists who have arranged to work with a particular sponsor affiliated with an institution that has the staff and facilities needed for the proposed training.

The Senior Faculty Fellowship. This award is designed to permit scientists to make major changes in the direction of their research careers, broaden their scientific background, and acquire new research capabilities.

Medical Scientist Training Program—(or the "M.D./Ph.D. Program"). This program, offered by the National Institute of General Medical Sciences (NIGMS), is supported at a small number of institutions (24) that have a history of high academic performance and significant evidence of prior research productivity. This six-year program to train individuals for both the M.D. and Ph.D. degree is one of the most effective means of developing and retaining clinical investigators. The experiment has worked. An analysis of the career of graduates between 1968 and 1978 has shown that these men and women moved rapidly up the academic ladder. A high percentage of the graduates rotated through clinical training before assuming a research career, but very few (only 4 of 301) elected to practice medicine.[4]

Short-Term Training. This program provides research training of students during summer months or in off-quarters. The purpose of this program—similar to the Post-Sophomore Opportunity—is to expose students to the advantages of a research career at an early stage in their development.

Slide 2 - Non-NRSA Manpower Development Programs (so-called "K series")

During the period of career development, the creative energies of young investigators are extremely high. The years near the end of the transition between supervised fellow to independent researcher tend to be very productive. Therefore, the NIH provides support for advanced preparation for the independent conduct of research to those capable of contributing to a body of scientific knowledge while they acquire experience in specific areas. Several programs are

available for these young investigators who require minimum supervision during this period when the direction of their future scientific careers is being established.

Special Emphasis Research Career Award is a five-year award, with up to $30,000 per year salary plus fringe benefits and some research support. It provides the opportunity for an individual to acquire experience in broad fundamental and clinical scientific disciplines essential for a multidisciplinary approach to the study of a very specific disease or medical problem. It is offered by NIA, NHLBI, DRR, NICHD and NIADDK.

The Academic Award also provides up to $30,000 per year salary plus fringe benefits and some research funding. This five-year award is designed to provide a stimulus for research development or improvement in a curriculum in specific medical or scientific disciplines that enhance an institution's environment for research. The awards are through the NIA, NIAID, NCI, NIEHS, NHLBI and NINCDS.

The Clinical Investigator Award. This five-year award is open only to physicians and provides up to $30,000 per year salary plus fringe benefits and some research support. Its purpose is to encourage newly-trained clinicians to develop basic and clinical research interests and capability in specific areas. It is offered by the NIA, NIAID, NIADDK, NICHD, NHLBI and NIEHS.

Career Conversion Award. This three-year award is offered only by the NIEHS and provides an annual salary of up to $30,000 plus fringe benefits and some research support. It is designed to facilitate the movement of individuals with research expertise in one scientific area to a career in a new discipline redirecting their research efforts to fields which require immediate investigation.

Research Career Development Award. This five-year award is a special salary grant to expedite the development and productivity of the country's most promising investigators. It is designed for individuals whose demonstrated research capability is such that their institutions are willing to free them from heavy teaching loads, committee assignment, service and administrative duties so that they can devote substantially full time to research. The award provides up to $30,000 per year in salary and fringe benefits.

These two slides attest to NIH's cardinal interest in maintaining a community of trained research scientists and the necessary flexibility in training opportunities. But, simply setting up the programs is not sufficient—they need to be assessed and examined on an ongoing basis and readjusted where necessary and when possible.

(LIGHTS)

It has been a concern to NIH that the distribution of NRSA support (those listed on my first slide) among postdoctoral students is now 70 percent to "academic" postdoctorals and 30 percent to "professional" postdoctorals (meaning

M.D.'s, D.D.S. and D.V.M.). Studies show that nearly 70 percent of the non NRS awards (those listed on my second slide) are made to holders of the Ph.D. degree.

It is not only the NIH that is concerned about clinical investigators—so are the AAMC and the AFCR. For the past several years, the Congress too has been interested and concerned. The House Appropriations Committee Report on the FY 1983 budget for the NIH, issued September 26,[5] stated: "The Committee shares the concerns that have been expressed by official and public witnesses about the difficulty of recruiting and retaining physicians for research careers, especially as all clinical research, involving human patients, must be done by—or at least under the guidance and supervision of—a qualified physician. It is apparent and understandable, that young physicians considering careers in health research are often dissuaded from applying for research training or research fellowships by their perception of the instability of the Federal commitment to research and by their awareness that a research career represents a substantial financial sacrifice when compared with almost any form of medical practice."

In response to such concerns expressed by the Congress in the past, NIH has made some changes in its training programs. For example, increases in stipend levels have been proposed; consideration is being given to expanding somewhat the successful program for MD/PhD's; the post-sophomore fellowship was instituted; review of applications has been streamlined; and the Special Training for Clinical Investigators Program has been instituted.

This year, again, the Congress has asked NIH to review its programs and suggest what steps might be taken to increase the number of young physicians who will apply for research training and to retain those who do embark on research careers. NIH would welcome, during this next year, comments and suggestions from this society and others in the scientific community.

For a number of years, the shortage and support of clinical investigators has been widely bemoaned. But how severe is this "shortage?" And how bad is the situation?

Slide 3 - Number of M.D. Principal Investigators on all R01 Grants Compared with the Number of M.D.'s Who Graduated 11 Years Previously.

In order to construct this slide, we displayed the number of M.D.'s serving as principal investigators on NIH investigator-initiated grants from 1968 to 1980. Against that, we plotted the number of M.D. graduates for each year starting in 1957. The 11-year gap reflects the fact that on average, the M.D. in research does not receive his or her first independent research grant until 11 years after graduation. As the slide shows, the ratio between M.D. principal investigators and number of M.D. graduates did not widen too dramatically over the years. However, since medical school enrollment increased greatly after 1968, we suspect that this gap has widened.

Although physician participation in research (in terms of actual numbers of researchers) took a big dip in the middle of the last decade, since then their participation has been gradually on the increase.

Because career participation in research for a physician is pretty much equated with a faculty appointment to a medical school, we can look to data on medical school faculties for some clues about the future. A recent analysis by NIH[6] (in press) shows that the percentage of all newly-hired physicians with postdoctoral research training, which fell from 28 percent in 1970 to a low of 20 percent in 1979, has since risen to 25 percent in 1981. This could be a positive sign for the future of clinical research.

At this time, NIH cannot fully assess the numbers of physicians involved in NIH-supported research. We think that many participate on large program project grants where they are working in roles other than principal investigators and thus cannot be counted by our tracking systems. Most likely they are subproject directors or participants in clinical portions of the multipart grants.

And, it is not at all certain whether a true count would be useful. I do not think that NIH could estimate that number of physician investigators who ought to be involved in research. But it is necessary to ensure some level of participation lest we miss out on important contributions to science and important advances in medicine that can only be provided by the perspective of the physician scientist.

Slide 4 - Number of Principal Investigators on All R01 Grants Holding M.D., Ph.D. or MD/PhD Degrees.

This slide shows, over the years, the rise in the number of grants going to Ph.D.'s and the number going to M.D.'s dropping through 1973 and now just beginning to recover. MD/PhD's (and these, of course, are in much smaller numbers) are holding rather steady. The rise in awards to PhD's coincided with the rapid expansion of the NCI and the large thrust into many areas of basic science.

Slide 5 - P.I.'s Holding M.D., Ph.D. or MD/PhD Degrees as a Percentage of All P.I.'s on R01 Grants.

This slide shows M.D., Ph.D. and MD/PhD principal investigators as a percentage of all PI's. The percentage of Ph.D.'s has risen steadily over the years, while as a percentage of all PI's, the percentage of M.D.'s has fallen rather precipitously. MD/PhD's have barely held even. These data are, of course, a consequence of the events shown on the previous slide.

Slide 6 - Success of New Applicants on NIH Research Projects by Type of Degree of the Principal Investigator.

The next two slides show the success rates for M.D.'s, Ph.D.'s and MD/Ph.D's applying for their first NIH research grants ("success rate" meaning that their grants were funded).

This slide shows that back in the early 1970's, M.D.'s had a greater success rate than Ph.D.'s but that in the mid-1970's, Ph.D.'s began to outstrip M.D.'s. Since then, Ph.D.'s have had consistently higher success rates. The MD/PhD is the most successful among the three types of principal investigators.

Slide 7 - Success Rates of New M.D., Ph.D., and MD/PhD Applicants Compared wtih Average Success Rates of All Type R01 Applicants in the Same Year.

This slide shows that success rates of M.D. applicants fell below average in about 1973 and have not come up to the average since then. In 1980, M.D.'s had a 30 percent success rate compared to the average, while Ph.D.'s had a 38 percent success rate and MD/PhD's, had the best record, a 43 percent success rate.

In order to discover why applications to NIH for grants to conduct clinical research may either be disapproved or receive poor priority scores in the review process, the Division of Research Grants recently examined the reviews of 256 applications rated by 13 different study sections.[7] For the study, clinical research was narrowly defined as research involving human subjects that include a doctor-patient relationship. The data confirmed the widespread impression that clinical research has a tougher time in the peer review system.

This study, which was similar to others done in 1960, 1961 and 1970, involved examination of study section summary statements or "pink sheets," by raters who assigned criticisms of the proposed research into the broad categories of faults summarized on the next slide.

Slide 8 - Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

This slide shows the shortcomings in poorly rated or disapproved grant applications for clinical research. It is both interesting and important to note that investigator qualifications and resources available at their institutions played a very minor role in poor rating. Flaws in research design and conception of the hypothesis led to poor scores from reviewers.

The most frequent deficiencies—faulty or confused hypotheses and inappropriate experimental design—were the same flaws that were cited in the basic research proposals.

I do wonder whether the facile explanation of the greater inherent difficulty of working with human subjects is the entire answer to the lower approval rates for physicians. Science has become complex, the methods intricate and the training period long so that the physician, even after residency and a year's fellowship, remains less well-trained than the man or woman with a Ph.D. who has been training for a research career since the baccalaureate. Thus the adequacy of the training opportunity must be a paramount consideration for the young physician.

The necessity for keeping NIH training programs healthy—and open—and attractive to young clinical investigators, is clear. There are only few data available, but one study by the AAMC[8] has shown that for both M.D.'s and Ph.D.'s postdoctoral training has the greatest influence on approval rate on first research grant applications. Other significant factors included the institution conferring the degree and the place of employment.

For the group of M.D.'s studied, having postdoctoral training raised approval rates from 55 percent to 72 percent. A basic conclusion from this study, which examined many possible influences on research grant success of medical school faculty, concluded: "The strongest finding....was the association between postdoctoral training and subsequent research capability. The need for continued postdoctoral training opportunities is strongly implied if the nation is to continue to promote and benefit from excellence in research."

Slide 9 - Success of Competing R01 Applications from Persons Completing Postdoctoral NRSA Training in 1977 and 1978.

(NEXT SLIDE)

A recent review by NIH of grant files[9] indicates the worth of NRSA training for both post-M.D. and Post-Ph.D. applicants.

There is no clear pattern of superiority in award rate for MD's and PhD's who have had NRSA training—MD's and PhD's award rates are generally equal. Some of the trainees, however, produced applications before completing training. These applications, as might be expected, are not as successful as those after training.

Slide 10 - Approval and Award Rates for All Competing R01 Applications

In this slide it is clear that MDs fare as well as PhDs in approval and funding. These last two slides suggest that there is no bias against clinical investigators in study sections when one compares people with roughly equivalent training experience.

This brings me to the heart of our concern about training for physician-scientists. The number of M.D.'s in research training supported by the NIH has fallen from about 4,100 in 1968 to about 1,800 in 1980. The reasons suggested for the decline in M.D. applicants for training are many. Whatever the reasons, if we do not heed this issue we will lose important contributions to science and necessary advances in medicine. The matter is complex, and needs to be addressed by NIH, the Congress, the medical schools, and societies such as this one.

These last comments should not be a disincentive to young investigators. It is important to note especially for the uncommitted student, resident or fellow, that although fewer M.D.'s are applying for training grants, the success rate for those who do apply remains as high as in the past and equals that of Ph.D. applicants.

The perspectives of the physician and the Ph.D. scientist inevitably differ. The physician has a broad acquaintance with many areas in the behavioral and biomedical sciences. Thus, the physician scientist has a very special role both in identifying relevant medical questions and in applying new knowledge to the investigation of disease. These roles cannot adequately be filled by Ph.D. scientists, however seminal and essential their contributions may be. The future of clinical science depends upon the quality and the number of new research leaders in the field. The quality is unquestionably there; potentially, so are the numbers.

Although we are unable to quantify the proper balance between clinical research and basic research, or between M.D. investigators and Ph.D. investigators, we do know that we need those precious few in our profession. I hope that through groups such as this, young people will be convinced of the excitement of clinical research, the importance of adequate training as a basis for their careers in research, and availability of the programs to ensure their necessary training and subsequent support. We have an ethical imperative to wed the laboratory and the clinic; only the clinical investigator can do this.

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[1]John A. Oates, M.D., Professor of Medicine and Pharmacology, Vanderbilt University School of Medicine, "Clinical Investigation: A Pathway to Discovery," address before the Association of American Physicians, May 1982.

[2]John W. Gardner, "Excellence: Can We Be Equal and Excellent Too?", Harper & Row, Publishers, New York and Evanston, 1961.

[3]NIH Program Evaluation Report: On the Status of Medical School Faculty and Clinical Research Manpower 1968-1990, NIH publication No. 82-2458, "A Report to the Clinical Sciences Panel of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel," National Academy of Sciences, National Research Council, April 30, 1981.

[4]National Institute of General Medical Sciences Report on Medical Sciences Program, December 27, 1978.

[5]Report No. 97-894, 97th Congress, 2nd Session, House of Representatives, "Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 1983," September 29, 1982.

[6]Charles R. Sherman, Ph.D. and George Bowden, "Updated Trends and Some New Observations About Medical School Faculties," Office of Program Planning and Evaluation, NIH, October 1982.

[7]Janet Cuca, "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapproval," Division of Research Grants, NIH, September 1982.

[8]"Education Patterns and Research Grant Success of Medical School Faculty," An evaluation study prepared for the NIH by the Association of American Medical Colleges, January 1979.

[9]"OPPE Program Analysis Note No. 6," "Competing Grant Applications From NRSA Trainees," Office of Program Planning and Evaluation, Office of the Director, NIH, October 1982.

Selected National Research Service Award Programs (NRSA)

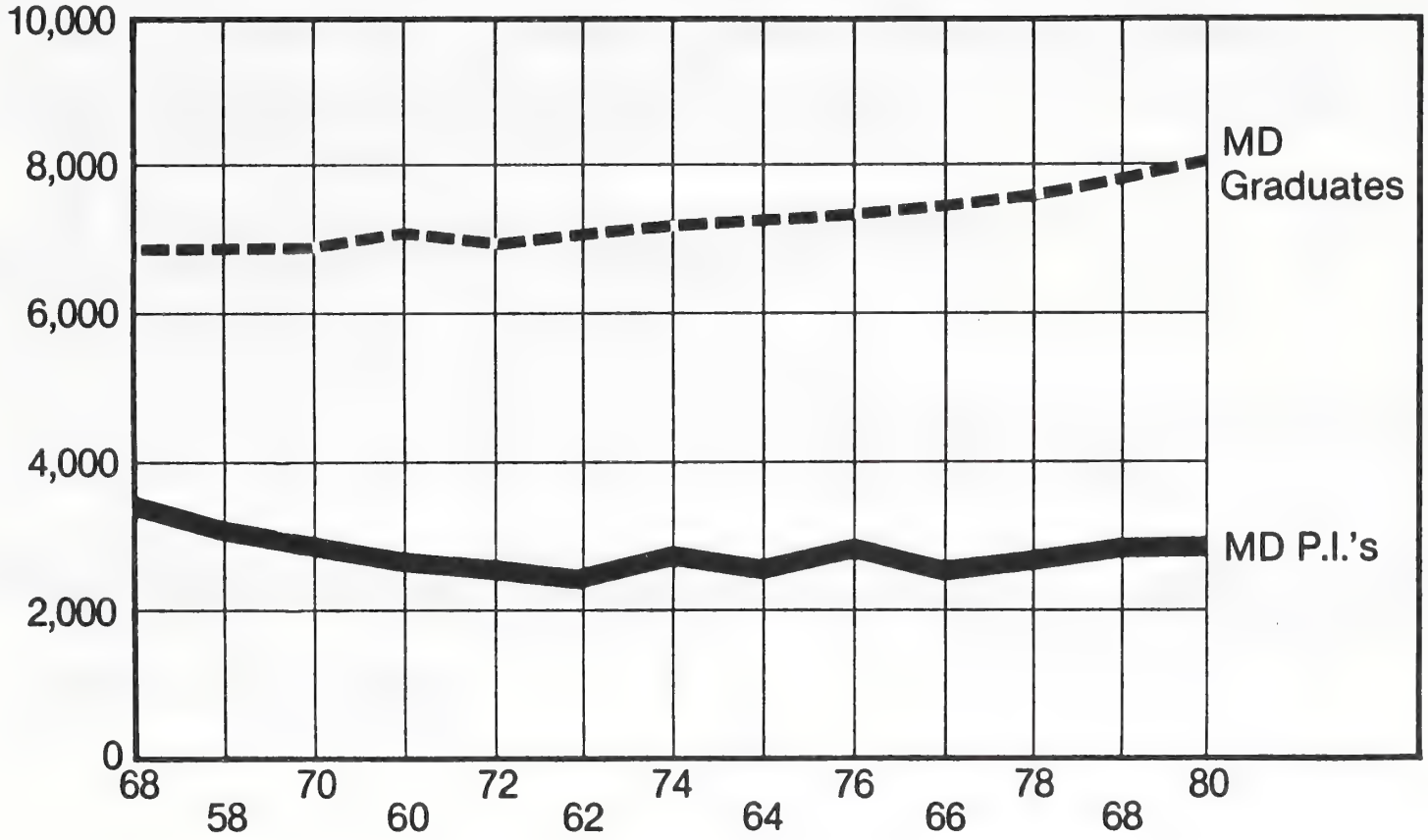
- Institutional Training Grant (Post-Sophomore Opportunity)
- Individual Fellowship
- Senior Faculty Fellowship
- Medical Scientist Training Program
- Short-Term Training

Non-NRSA Manpower Development Programs

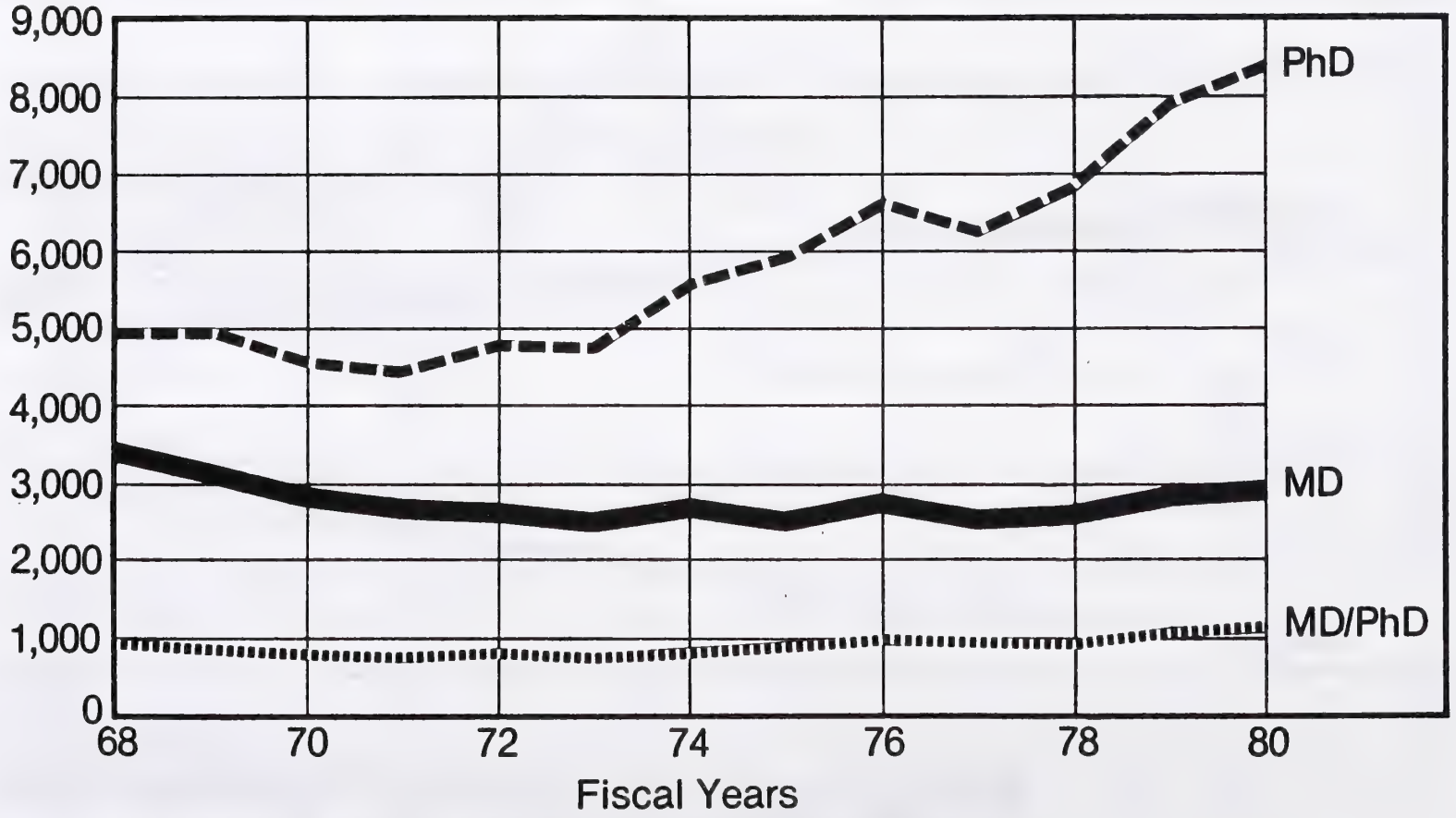
- Special Emphasis Research Career Award
- Academic Award
- Clinical Investigator Award
- Career Conversion Award
- Research Career Development Award
- New Investigator Research Award

Number of MD P.I.'s on All R01 Grants Compared with Number of MD's who Graduated Eleven Years Previously

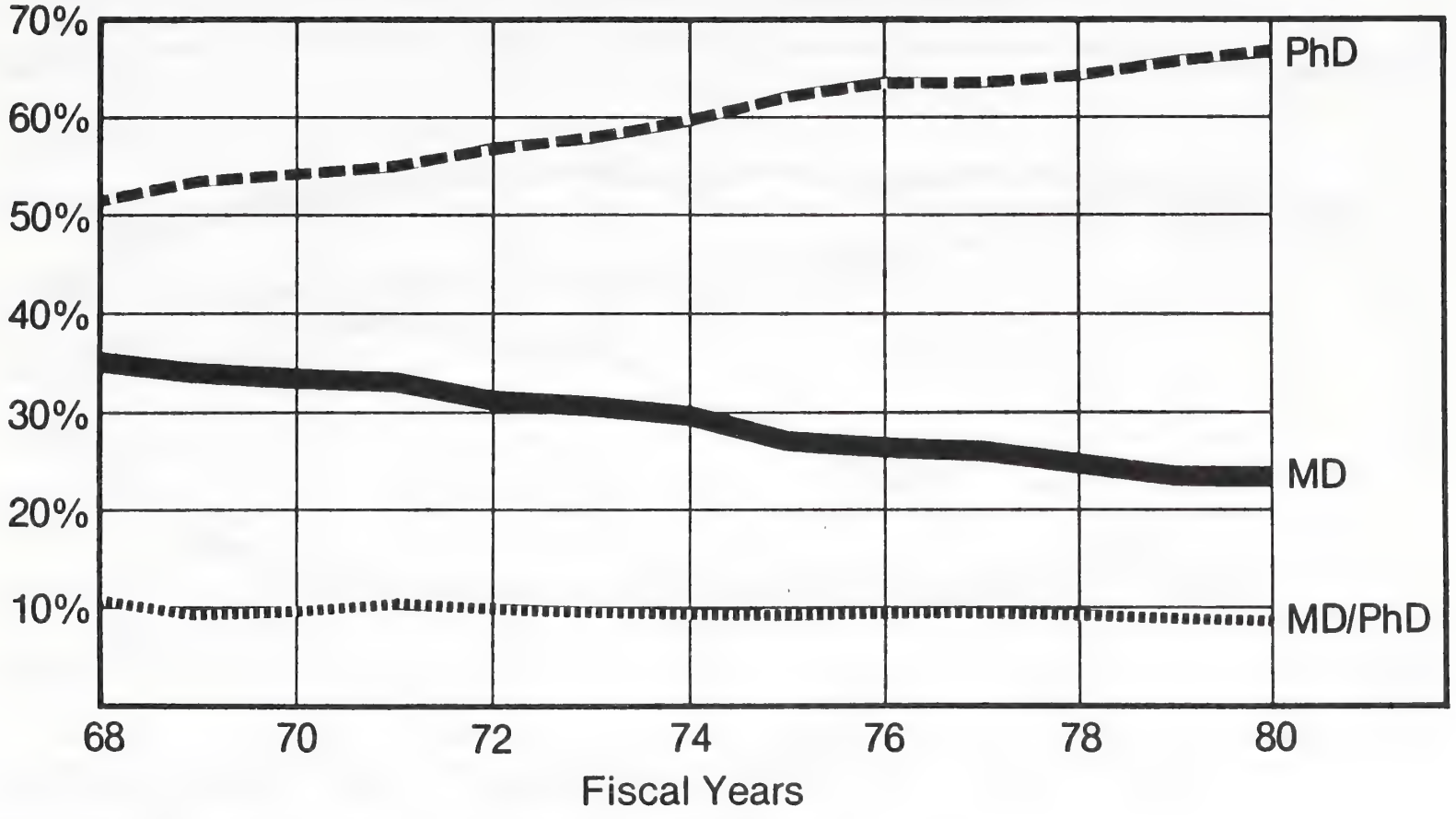
(Average Interval of 11 Years between Medical School Graduation and Beginning of First Grant per Douglass and James [Science 7/20/73])



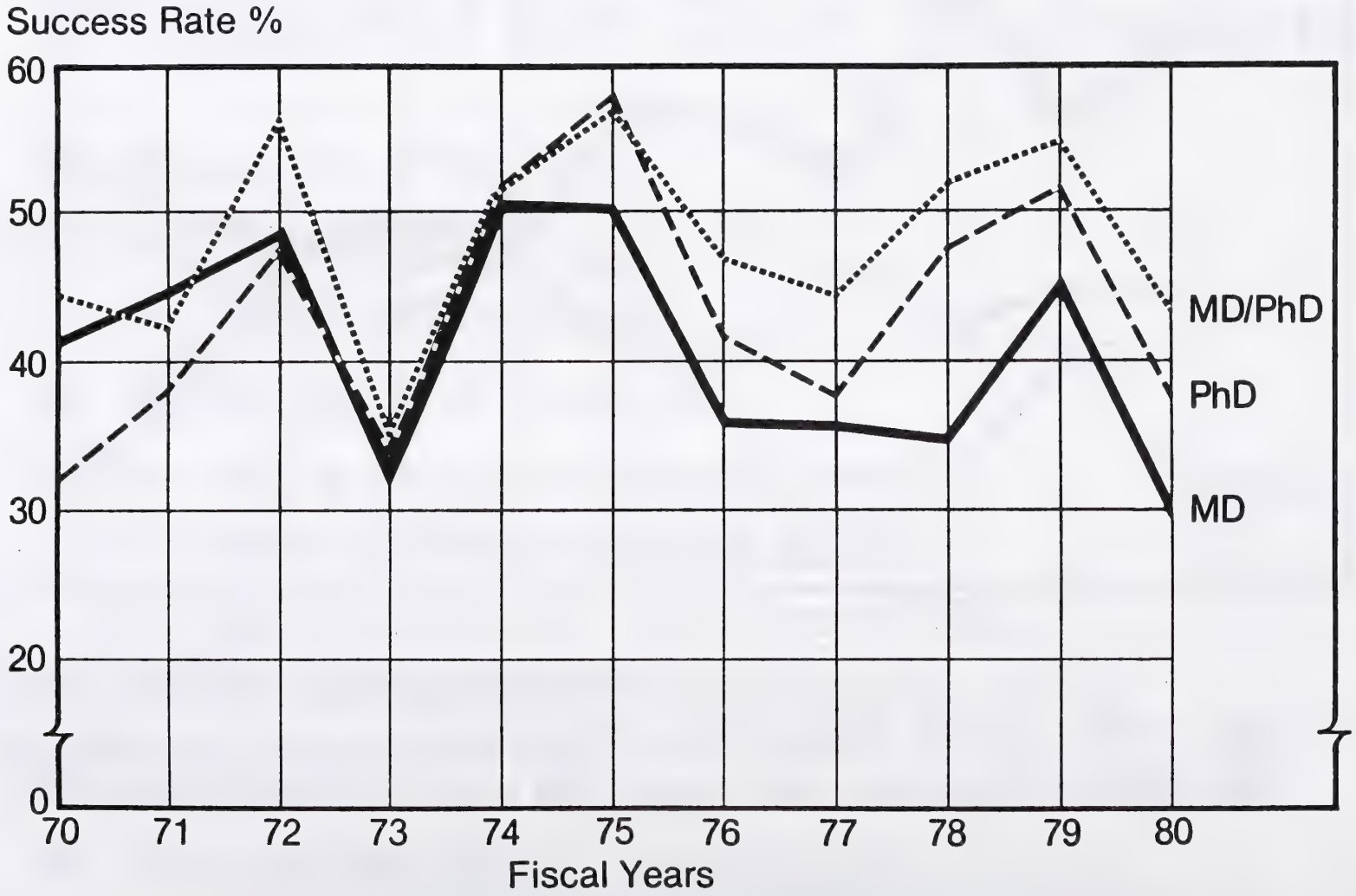
Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



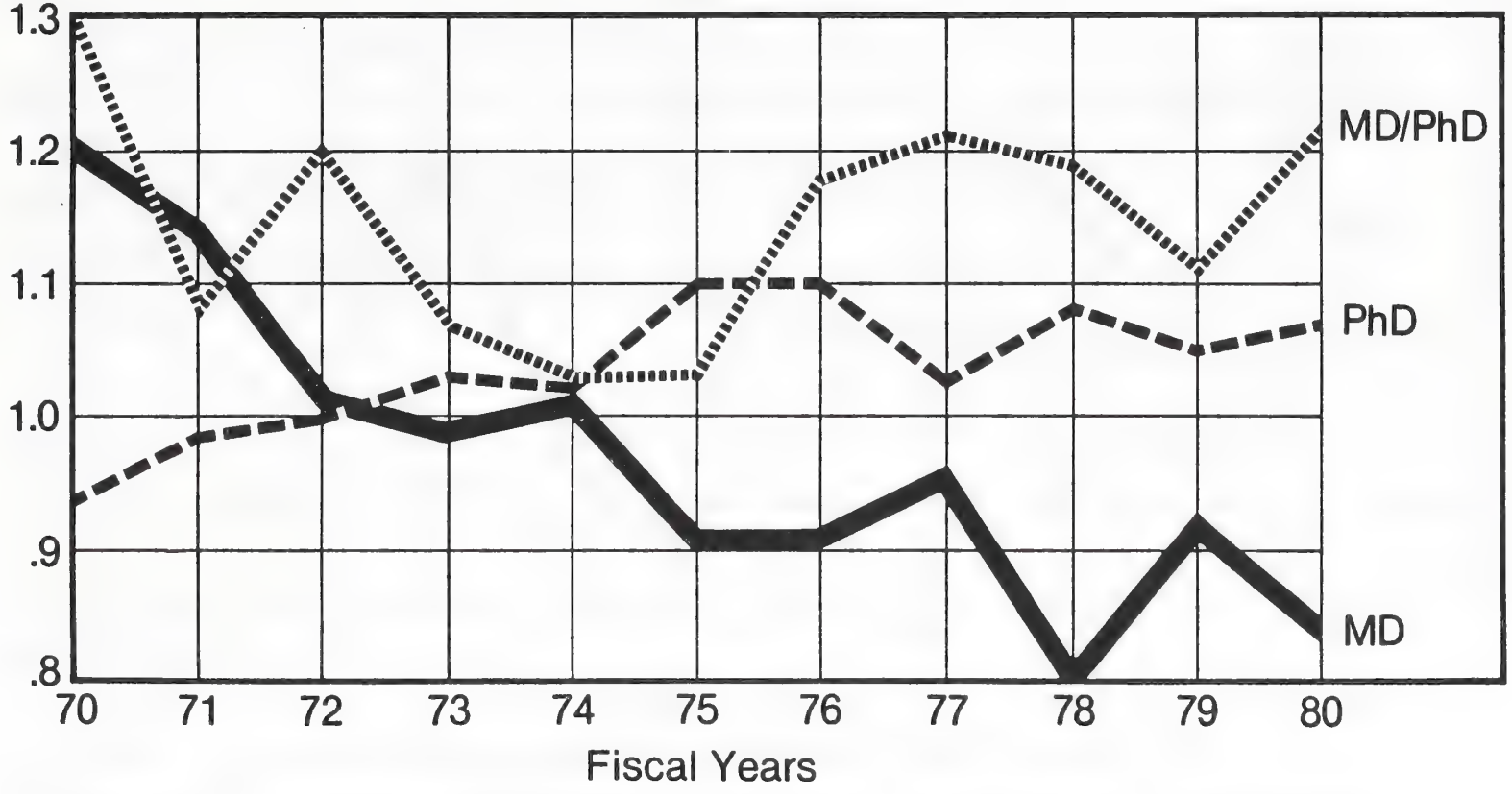
P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants



Success of New Applicants on NIH Research Projects (Type 1 R01 Applicants by Type of Degree of P.I.)



Success Rates of New MD, PhD and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year



Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - Hypothesis (47%)
  - Significance (30%)
- Experimental Design:
  - Study Group or Controls (40%)
  - Technical Methodology (66%)
  - Data Collection Procedures (41%)
  - Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

Success of Competing R01 Applications from Persons Completing Postdoc NRSA Training in 1977 & 1978. FY 1973 – FY 1981

Post-PHD

FY	Applications	Award Rate Percent
1973-77*	49	30
1977	43	45
1978	165	52
1979	292	59
1980	316	45
1981	361	40

Post-MD

FY	Applications	Award Rate Percent
1973-77*	14	57
1977	12	67
1978	48	43
1979	77	56
1980	118	40
1981	113	42

*Applications before completion of training.

Approval and Awards Rates for Competing R01 Applications: 1974-1980

	Approval Rate		Award Rate	
FY	M.D.	Ph.D.	M.D.	Ph.D.
1974	73.9	78.9	60.7	56.0
1975	72.0	77.4	59.5	60.2
1976	67.7	73.8	50.4	47.2
1977	72.0	76.0	41.2	36.8
1978	74.4	80.2	44.1	45.5
1979	76.1	79.4	51.1	51.7
1980	76.7	81.0	41.5	41.7

KEYNOTE ADDRESS

LITA ANNENBERG HAZEN AWARDS LUNCHEON*

by

JAMES B. WYNGAARDEN, M.D.**

FOR SEVERAL SPECIFIC REASONS, I AM PARTICULARLY PLEASED TO BE A PARTICIPANT IN THESE PROCEEDINGS. FIRST, BECAUSE I HAVE SUCH A HIGH REGARD FOR THE CONCEPT OF THE "LITA ANNENBERG HAZEN AWARD FOR EXCELLENCE IN CLINICAL RESEARCH" AND FOR MRS. HAZEN'S SUPPORT THAT MAKES IT POSSIBLE. AMONG THE SEVERAL MAJOR AWARDS FOR ACCOMPLISHMENT IN THE FIELDS OF MEDICINE AND SCIENCE, IT IS UNIQUE AND STANDS OUT AS A MODEL FOR GENEROUS AND PRACTICAL RECOGNITION OF SUCCESSFUL EFFORT. IT NOT ONLY REWARDS WHAT HAS BEEN DONE, BUT PROVIDES SUBSTANTIAL ASSISTANCE TO ITS RECIPIENTS AS THEY CONTINUE THE QUEST TO WHICH THEY HAVE DEVOTED THEIR CAREERS.

ANOTHER REASON FOR MY ENTHUSIASM ABOUT THE HAZEN AWARD IS ITS TIMELY FOCUS ON CLINICAL RESEARCH--A SUPREMELY IMPORTANT FACET OF BIOMEDICAL RESEARCH. THE RECOGNITION AND ENCOURAGEMENT IT GIVES ARE BOUND TO HAVE A POSITIVE EFFECT AT A TIME WHEN THERE IS WIDESPREAD

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*The Lita Annenberg Hazen Award for Excellence in Clinical Research, The Carlyle Hotel, New York, New York, November 9, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

CONCERN ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS.

SINCE COMING TO MY PRESENT POSITION AT THE NATIONAL INSTITUTES OF HEALTH, I HAVE BECOME EVEN MORE STRONGLY CONVINCED THAN BEFORE OF THE VITAL IMPORTANCE OF ATTRACTING THE BEST AND BRIGHTEST TO CAREERS IN RESEARCH--ESPECIALLY THE NEED TO INTEREST AND HOLD YOUNG MEN AND WOMEN WHO ARE TRAINED AS PHYSICIANS. IN MY STATEMENTS TO TOP OFFICIALS IN THE ADMINISTRATION, TO THE CONGRESS AND TO THE PUBLIC, THE NEED HAS BEEN A RECURRENT THEME--AND I PLAN TO CONTINUE THIS EMPHASIS.

AT THE TIME THE PRIZE WAS FIRST ANNOUNCED, TOM CHALMERS WROTE OF A PURPOSE OF THE AWARD BEYOND THE INDUCEMENT IT OFFERS TO YOUNG INVESTIGATORS. IN AN EDITORIAL THAT APPEARED IN THE NEW ENGLAND JOURNAL IN MAY 1979, TOM SAID, "IT IS HOPED THAT THESE AWARDS WILL ALSO STIMULATE A NATIONAL DIALOGUE THAT WILL RESULT IN A DIVERSION OF MORE PRIVATE AND HEALTH CARE FUNDS TO THE TRAINING AND SUPPORT OF PHYSICIANS WHO WILL DEVOTE THEIR CAREERS TO CLINICAL AND BASIC RESEARCH. AN EXTRA BILLION DOLLARS SO SPENT COULD NOT ONLY SAVE MORE THAN A BILLION HEALTH-CARE DOLLARS PER YEAR, BUT LEAD TO A MORE IMPORTANT GOAL: IMPROVING THE QUALITY OF LIFE."[1]

IN ITS UNIQUE WAY, THE LITA ANNENBERG HAZEN AWARD IS INDEED A STRONG AND ELOQUENT STATEMENT ON THE IMPORTANCE OF CLINICAL INVESTIGATION.

NOT THE LEAST OF MY REASONS FOR BEING PLEASED TO PARTICIPATE IN THIS OCCASION IS THE FACT THAT THE AWARD IS TO BE GIVEN TO MY FRIENDS AND COLLABORATORS, JOE GOLDSTEIN AND MIKE BROWN.

SINCE BOTH OF THEM SPENT THE EARLY PART OF THEIR RESEARCH CAREERS AT THE NIH, I AM HAPPY TO BE ABLE TO SPEAK ALSO FOR THEIR FORMER ASSOCIATES IN BETHESDA IN EXTENDING OUR WARMEST CONGRATULATIONS TO THEM.

LET ME SAY A WORD ABOUT THAT COLLABORATION. SOME OF YOU MAY KNOW THAT JOHN STANBURY, DON FREDRICKSON, AND I HAVE BEEN INVOLVED AS EDITORS IN PRODUCING SUCCESSIVE EDITIONS OF A RATHER LARGE REFERENCE BOOK FOR CLINICIANS AND RESEARCHERS ("Metabolic Basis of Inherited Disease"). IN THE PREFACE TO THE FIFTH EDITION, AFTER COMMENTING ON THE NEED TO ACCOMMODATE THE REVOLUTIONARY CHANGES IN THE FIELDS OF MOLECULAR BIOLOGY AND IMMUNOLOGY, WE NOTED THAT "FROM ONE STANDPOINT, THE MOST IMPORTANT RECENT CHANGE MADE TO COPE

WITH THE CONTEMPORARY CHALLENGE AND TO PREPARE FOR THE FUTURE IS TO INCREASE THE NUMBER OF THE EDITORS TO FIVE. THE THREE "SENIOR" EDITORS WARMLY WELCOME JOSEPH GOLDSTEIN AND MICHAEL BROWN INTO HARNESS AND ACKNOWLEDGE THEIR INVALUABLE INFLUENCE ON THIS EDITION."[2]

MAY I MAKE THE SLIGHTLY BOASTFUL OBSERVATION THAT "WE FOUND THEM FIRST." IN FACT, I FIRST FOUND MIKE BROWN WHEN HE WAS A MEDICAL STUDENT AT THE UNIVERSITY OF PENNSYLVANIA AND I A TEMPORARY CHAIRMAN THERE. I FIRST MET JOE GOLDSTEIN A FEW YEARS LATER.

I COULDN'T BE MORE PLEASED ABOUT THIS DESERVED RECOGNITION FOR JOE AND MIKE.

THEIR WORK EPITOMIZES EXCELLENCE IN BASIC AND CLINICAL INVESTIGATION, AND THIS RECOGNITION CONVEYS IN THE FULLEST THE DESIRED STATEMENT OF ENCOURAGEMENT TO THE PROFESSIONAL AND SCIENTIFIC COMMUNITY.

A BIT EARLIER, I SPOKE OF CONCERN ABOUT CAREER CHOICES BY YOUNG PHYSICIANS--AND THE NEED TO ENCOURAGE MORE OF THEM TO ENTER RESEARCH.

JUST A FEW DAYS AGO, WE RECEIVED THE REPORT OF THE HOUSE COMMITTEE ON APPROPRIATIONS REGARDING THE PROPOSED 1983 BUDGET FOR THE NATIONAL INSTITUTES OF HEALTH--PERMIT ME TO READ A PARAGRAPH.

"THE COMMITTEE SHARES THE CONCERNS THAT HAVE BEEN EXPRESSED BY OFFICIAL AND PUBLIC WITNESSES ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS, ESPECIALLY AS ALL CLINICAL RESEARCH INVOLVING HUMAN PATIENTS MUST BE DONE BY--OR AT LEAST UNDER THE GUIDANCE OF--A QUALIFIED PHYSICIAN. IT IS APPARENT AND UNDERSTANDABLE THAT YOUNG PHYSICIANS CONSIDERING HEALTH CAREERS ARE OFTEN DISSUADED FROM APPLYING FOR RESEARCH TRAINING OR RESEARCH FELLOWSHIPS BY THEIR PERCEPTION OF INSTABILITY IN THE FEDERAL COMMITMENT TO RESEARCH AND BY THEIR AWARENESS THAT A RESEARCH CAREER REPRESENTS A SUBSTANTIAL SACRIFICE WHEN COMPARED WITH ALMOST ANY FORM OF MEDICAL PRACTICE. THE COMMITTEE WOULD LIKE NIH TO REVIEW THIS PROBLEM CAREFULLY AND TO SUGGEST WHAT STEPS MIGHT USEFULLY BE TAKEN TO INCREASE THE NUMBER OF YOUNG PHYSICIANS WHO WILL APPLY FOR RESEARCH TRAINING AND TO RETAIN THOSE WHO DO EMBARK ON RESEARCH CAREERS. THE COMMITTEE WILL EXPECT A REPORT ON THIS SUBJECT AT NEXT YEAR'S HEARINGS."[3]

EVEN WITHOUT THAT PRODDING, WE HAVE DEVOTED CONSIDERABLE ATTENTION TO THIS PROBLEM AND HAVE UNDER CONSIDERATION SOME MAJOR STEPS TOWARD ITS SOLUTION. YOU MAY BE SURE THAT THE PREPARATION OF THIS REPORT WILL RECEIVE OUR MOST CAREFUL ATTENTION.

IN THE PORTION OF THE REPORT PRECEDING THE STATEMENT ON CLINICAL RESEARCH, THE COMMITTEE EXPLAINED ITS DECISION TO INCREASE THE APPROPRIATION REQUESTED FOR ALL RESEARCH TRAINING PROGRAMS BY OVER $18 MILLION TO PROVIDE FOR A TOTAL OF 10,000 TRAINEES--A LEVEL PERCEIVED BY THE COMMITTEE AS BARELY LARGE ENOUGH TO BALANCE INEVITABLE ATTRITION FROM ACTIVE PARTICIPATION IN RESEARCH. BEAR IN MIND, HOWEVER, THAT THE APPROPRIATIONS FOR RESEARCH TRAINING, WHATEVER THE FINALLY APPROVED AMOUNT, WILL FUND TRAINING PROGRAMS FOR BOTH PH.D.s AND M.D.s. WHILE STABILITY--IN THE SENSE OF ASSURING A PREDICTABLE SOURCE OF SUPPORT FOR RESEARCH TRAINING IS ESSENTIAL--OTHER FACTORS HAVE SUBSTANTIAL IMPACT ON DECISIONS BY YOUNG PHYSICIANS WHETHER OR NOT TO ENTER RESEARCH AS A CAREER.

ONE SUCH DECISION FACTOR IS THE YOUNG M.D.'s PERCEPTION OF THE LONG-TERM STABILITY OF FEDERAL SUPPORT OF RESEARCH. IF THE OPPORTUNITY TO ENGAGE IN SUPPORTED RESEARCH IS HIGHLY UNCERTAIN--THE YOUNG PHYSICIAN COULD REASONABLY QUESTION THE WISDOM OF UNDERTAKING RESEARCH TRAINING. THIS IS A MAJOR REASON FOR OUR CONTINUED

EMPHASIS OF THE NEED TO "STABILIZE" OUR OFFERING OF GRANTS FOR INVESTIGATOR-INITIATED PROJECT RESEARCH--TO PROVIDE A REASONABLE DEGREE OF ASSURANCE ABOUT FUTURE OPPORTUNITIES. INCIDENTALLY, WE REACHED 5,030 NEW STARTS AND COMPETING RENEWALS IN FY 1982, ALMOST 300 MORE THAN ORIGINALLY PREDICTED. WE ACHIEVED THIS NUMBER BY FURTHER CUTBACKS OF OTHER MECHANISMS, SUCH AS CONTRACTS, CENTERS AND CLINICAL TRIALS.

WE RECOGNIZE THAT STABILIZATION, BOTH OF TRAINING GRANTS AND RESEARCH PROJECT GRANTS, WILL NOT OF ITSELF ASSURE AN ADEQUATE NUMBER OF CLINICAL INVESTIGATORS.

SOME INSIGHTS ON THE MOTIVATION OF MEDICAL STUDENTS CAN BE GAINED BY EXAMINATION OF THE RESULTS OF STUDIES CONDUCTED BY THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES.

IN DECEMBER 1979, THE AAMC DISTRIBUTED AN EXTENSIVE GRADUATION QUESTIONNAIRE TO ALL SENIOR MEDICAL STUDENTS. RESPONSES WERE RECEIVED FROM 10,215 STUDENTS, 67 PERCENT OF ALL SENIORS WHO WERE EXPECTED TO GRADUATE IN 1980.

THE AAMC, AS YOU KNOW, IS NOW ASKING MEMBERS OF EACH GRADUATING CLASS A NUMBER OF QUESTIONS ABOUT THEIR CAREER

PLANS. THE 1980 QUESTIONNAIRE, HOWEVER, INCLUDED A SUBSTANTIAL NUMBER OF QUERIES ABOUT CAREER MOTIVATION AND ATTITUDES.

I WILL NOT ATTEMPT TO SUMMARIZE THE RESULTS OF THE 1980 STUDY BUT MERELY POINT OUT A FEW INTERESTING FINDINGS, MORE OR LESS AT RANDOM:[4]

GENERAL DATA ARE AVAILABLE FROM A SAMPLING IN 1960, AND FROM QUESTIONNAIRES SENT TO ALL SENIORS IN 1978, 1979, 1980, AND 1981. IN 1960, THE PROPORTION OF SENIORS CHECKING A PREFERENCE FOR RESEARCH AND/OR TEACHING--OR A COMBINATION OF RESEARCH, TEACHING, AND PRACTICE--WAS 39 PERCENT AS COMPARED WITH 22.4 PERCENT FAVORING RESEARCH CAREERS IN 1978, 20.3 PERCENT IN 1979, 21.8 PERCENT IN 1980, 23.2 IN 1981, AND 22.2 PERCENT IN 1982.

A RETROSPECTIVE STUDY OF THE 1960 CLASS SHOWED THAT LESS THAN HALF (44 PERCENT) OF THE GRADUATES THEN MENTIONING RESEARCH AS A PREFERENCE DID IN FACT GO ON TO CONDUCT AND PUBLISH RESEARCH.

AS AN INTERESTING AND POSSIBLY SIGNIFICANT SIDELIGHT, THE STUDY TURNED UP THE FACT THAT 12 PERCENT

OF THE CLASS OF 1960 WHO SAID THEY DID NOT INTEND TO GO INTO RESEARCH LATER CHANGED THEIR MINDS AND DID SO.

OF COURSE, WE DO NOT KNOW HOW MANY OF THE CLASS OF 1982 WILL FULFILL THEIR EXPRESSED PLANS--BUT IT WOULD TAKE A VERY HIGH PROPORTION TO RESULT IN THE SAME LEVEL OF PARTICIPATION AS THE CLASS OF 1960.

NOT SURPRISINGLY, THE STUDY FOUND THAT THE AVAILABILITY OF RESEARCH TRAINING SUPPORT WAS AMONG THE IMPORTANT FACTORS INFLUENCING THE SENIORS' CHOICE TO PROCEED WITH A RESEARCH CAREER, AND, CONSEQUENTLY, IT COULD BE INFERRED THAT A LOSS OF SUCH OPPORTUNITIES COULD DIMINISH THE ALREADY SMALL PROPORTION OF GRADUATES PROCEEDING ON TO RESEARCH CAREERS.

BUT THE AVAILABILITY OF RESEARCH TRAINING SUPPORT WAS ONLY FOURTH IN THE LIST OF FACTORS INFLUENCING SENIORS WHO LOOK TO RESEARCH CAREERS. THE THREE FACTORS OF HIGHEST IMPORTANCE TO THEM IN ORDER WERE:

- OPPORTUNITY TO WORK IN THE ACADEMIC COMMUNITY
- CHALLENGE OF SEARCH FOR NEW KNOWLEDGE
- RESEARCH EXPERIENCE WHILE A PREMEDICAL OR MEDICAL STUDENT

ALL OF THESE TOP PREFERENCES SUGGEST HOW MUCH INFLUENCE THE MEDICAL SCHOOL EXPERIENCE HAS, BOTH DIRECTLY THROUGH PROVIDING EXPOSURE TO RESEARCH AND INDIRECTLY THROUGH PRESENTING TO THE STUDENT AN ATTRACTIVE IMAGE OF THE ACADEMIC-RESEARCH CAREER.

ANOTHER SET OF FINDINGS FROM THE STUDY WAS SOMEWHAT SURPRISING. AS A WHOLE, THE 1980 SENIORS SAID THAT THEY CONSIDERED AS OF MINOR OR NO IMPORTANCE FOUR FACTORS GENERALLY ASSUMED TO BE DETERRENTS TO A RESEARCH CAREER:

- THE UNCERTAIN AVAILABILITY OF RESEARCH FUNDS AFTER COMPLETION OF TRAINING
- THE FINANCIAL DISADVANTAGES OF A RESEARCH CAREER
- THE OBLIGATION TO PAY BACK RESEARCH TRAINING BY CONTINUED RESEARCH ACTIVITY

- THE INCREASING FRUSTRATION OF RESEARCHERS IN CONDUCTING CLINICAL RESEARCH

IN MY VIEW, ALL FOUR OF THESE POINTS LOOM MUCH LARGER A FEW YEARS LATER WHEN STUDENTS AS RESIDENTS OR FELLOWS FACE THE REALITIES OF A RESEARCH DECISION. IT IS HIGHLY LIKELY THAT FINANCIAL CONCERNS IN PARTICULAR WILL ASSUME MORE WEIGHT FOR THE SENIORS IN THE YEARS FOLLOWING GRADUATION FROM MEDICAL SCHOOL.

THE RESULTS OF THE STUDY STRONGLY SUGGEST, HOWEVER, THAT IF THE NECESSARY NUMBER OF CLINICAL INVESTIGATORS IS TO BE MAINTAINED IN THE COMING YEARS, UNDERGRADUATE MEDICAL STUDENTS SHOULD BE PROVIDED TIME AND OPPORTUNITY TO TRY RESEARCH AND SHOULD BE GIVEN A CLEAR UNDERSTANDING OF THE PROSPECTS FOR AND REWARDS OF ACADEMIC EMPLOYMENT. WITH THE REMOVAL OF PAYBACK OBLIGATION FOR THE FIRST YEAR OF NRSA SUPPORT, NIH ONCE AGAIN IS ABLE TO OFFER SUPPORT FOR A RESEARCH YEAR; E.G., A POST-SOPHOMORE FELLOWSHIP TO MEDICAL STUDENTS, AND WE INTEND TO DO SO.

IN ADDRESSING THE FRESHMAN CLASS AT GEORGETOWN UNIVERSITY'S SCHOOL OF MEDICINE THIS FALL, DEAN JOHN BERNARD HENRY MADE A STATEMENT THAT ONE COULD WISH HAD BEEN MADE TO EVERY FRESHMAN ENTERING MEDICAL SCHOOL THIS YEAR. LET ME REPEAT A PORTION OF IT.

HE SAID, "THE LABORATORY SELDOM SEEMS TO BECKON WITH THE SAME DRAMA AND EXCITEMENT AS THE HOSPITAL--BUT LET ME ASSURE YOU IT IS THERE. THE LABORATORY AND THE CLASSROOM ARE THE PARENTS OF MEDICINE. IT COULD NOT HAVE BEEN BORN WITHOUT THEM.

"ALL THAT THIS PROFESSION IS AND HAS BECOME IS BASED ON INVESTIGATION AND RESEARCH. SOMEONE, SOMEWHERE, SOMETIME HAD AN INQUIRING MIND AND THE INTELLIGENCE AND STICK-TO-IT-IVENESS TO LABOR LONG HOURS WITH ONE GOAL IN MIND: DISCOVERY! AND IT IS THEIR DISCOVERIES AND THEIR ACCOMPLISHMENTS THAT ENABLE US TO TREAT OUR PATIENTS AND EXERCISE OUR PROFESSION. WE WOULD HAVE NO KNOWLEDGE TO IMPART HAD SOMEONE NOT INVESTIGATED."

DEAN HENRY OBSERVED THAT "THE CLINICIAN RECEIVES THE GRATITUDE, UNDYING AFFECTION AND APPLAUSE OF HIS PATIENTS, BUT HIS COLLEAGUES KNOW ALL TOO WELL THAT HE HAS,

TECHNICALLY, PUT INTO 'PRACTICE' THE FRUITS OF SOMEONE ELSE'S 'LABOR.' I LIKE TO THINK THAT MAKES GOOD SENSE ETYMOLOGICALLY, FOR THE WORDS 'PRACTITIONER' AND 'LABORATORY' IMPLY PRACTICE AND LABOR."

FOR A MOMENT, PERMIT ME TO PUT ON THE LABORATORY COAT I HAVEN'T HAD OPPORTUNITY TO WEAR FOR SIX MONTHS OR SO AND SPEAK AS A SCIENTIST. NEVER BEFORE IN MY CAREER IN CLINICAL RESEARCH HAS EXCITEMENT SEEMED SO INTENSE--ABOUT ACCOMPLISHMENTS THAT HAVE BEEN MADE BY CLINICAL INVESTIGATORS AND FOR OPPORTUNITIES YET TO COME IN THE NEXT SEVERAL DECADES. A WELL-CONCEIVED EMPHASIS ON MAINTAINING A PRODUCTIVE COMMUNITY OF BASIC SCIENTISTS HAS PAID OFF IN TERMS OF THE STORE OF FUNDAMENTAL KNOWLEDGE NOW AT HAND. THE KNOWLEDGE ACCRUED IN JUST THE LAST 10 YEARS IN VIROLOGY, MOLECULAR BIOLOGY, PHARMACOLOGY, CELL BIOLOGY AND IMMUNOLOGY OPENS UP INFINITE OPPORTUNITIES FOR CLINICAL INVESTIGATORS. BEYOND THAT, CONTINUED RESEARCH ON HYBRIDOMAS, RECOMBINANT DNA TECHNOLOGY, AND ONCOGENES, FOR EXAMPLE, WILL SOON NEED--FOR FURTHER ADVANCEMENT--THE INPUT OF MORE CLINICAL INVESTIGATORS.

WHILE ACTIVE CONCERN FOR THE FUTURE OF CLINICAL RESEARCH IS THE OBLIGATION OF THE NIH, ACADEMIC MEDICINE, AND THE MEDICAL PROFESSION, THE CURRENT GENERATION OF

CLINICAL INVESTIGATORS HAS A SPECIAL RESPONSIBILITY TO PORTRAY THE SATISFACTIONS THAT CAN COME FROM CLINICAL RESEARCH AS A CAREER. THE DISINCENTIVES ARE GREAT FOR YOUNG PEOPLE IN THE THROES OF MAKING CAREER DECISIONS. MANY ARE DRAWN INTO CAREERS IN MEDICAL PRACTICE BECAUSE OF THE OPPORTUNITIES IT PRESENTS TO BE INSTRUMENTAL IN EASING PAIN, PREVENTING DISABILITY AND SAVING LIVES. WE NEED TO LET STUDENTS KNOW THAT IN MANY KINDS OF CLINICAL RESEARCH THERE IS OPPORTUNITY NOT ONLY TO BE A CAPABLE AND CARING CLINICIAN BUT ALSO TO SHARE IN THE EXCITEMENT THAT COMES FROM DISCOVERY.

BEYOND THE PERSONAL GRATIFICATION THAT COMES FROM CREATIVE WORK, CLINICAL RESEARCH OFFERS THE CHANCE NOT ONLY TO CONTRIBUTE TO THE HEALTH OF INDIVIDUAL PATIENTS, BUT ALSO, BY MAKING AND SHARING SCIENTIFIC CONTRIBUTIONS, TO BENEFIT WHOLE CLASSES OF PATIENTS. THOUGH THERE IS A NATURAL PULL TOWARD MEDICAL PRACTICE, WE MUST KEEP STRESSING THAT FOR THOSE EXCEPTIONAL STUDENTS WHO WILL TAKE ON THE CHALLENGE OF RESEARCH, THE REWARDS ARE GREAT.

I BELIEVE THAT OUR OWN WORDS AND ACTIONS AS CLINICAL INVESTIGATORS ARE CRITICAL TO THE FUTURE OF OUR PROFESSION. IN HIS BOOK, "EXCELLENCE; CAN WE BE EQUAL AND

EXCELLENT TOO?", JOHN GARDNER REMARKED THAT THE INFLUX OF EXCELLENT NEW PEOPLE INTO A GIVEN FIELD IN LARGE PART DEPENDS UPON THE MORALE OF THAT FIELD. AND A MAJOR COMPONENT OF OUR COLLECTIVE MORALE IS THE OPTIMISM AND ENCOURAGEMENT WE PORTRAY TO NEWCOMERS AND THOSE ON THE BRINK OF DECISION.

I CONFIDENTLY SPEAK FOR CLINICAL INVESTIGATORS, MEDICAL PRACTITIONERS, HEALTH EDUCATORS, RESEARCH FUNDING AGENCIES AND THE GENERAL PUBLIC AS WELL, IN EXPRESSING GRATITUDE TO MRS. HAZEN FOR THE WISDOM OF HER ACTION IN ESTABLISHING THE LITA ANNENBERG HAZEN AWARD.

Footnotes

[1] New England Journal of Medicine, May 10, 1979, p. 1109.

[2] The Metabolic Basis of Inherited Disease (5th ed.), 1982, Preface.

[3] Report 97-894, House of Representatives, 97th Congress (2nd Session), p. 28.

[4] Data from NIH Program Evaluation Report, "On the Status of Medical School Faculty and Clinical Research Manpower," Oct. 1981, pp. 7-9.

DIRECTIONS AND CHALLENGES IN HEALTH SCIENCES RESEARCH*

by

James B. Wyngaarden, M.D.**

I want to tell you first of all how pleased I am to be in North Carolina again. Although it is now more than six months since I moved to Bethesda, this area is still home to me. I am delighted to be here as Director of the National Institutes of Health to participate in the dedication of this magnificent facility--the first true home of the National Institute of Environmental Health Sciences since it was established 16 years ago this month--and to launch today's science program in which the achievements of NIEHS scientists will be presented.

This is a singular occasion for me--a coming together with members of both of my NIH and university families to talk about the great humanitarian adventure of which we are a part. This is an exquisitly exciting time in biomedical research and I am happy to be a part of the process of promoting its well-being and of insuring that its findings contribute to the health of people here and around the world.

The new campus of the National Institute of Environmental Health Sciences is an especially appropriate place in which to discuss directions and

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**Director, National Institutes of Health, Bethesda, Maryland 20205

challenges in health sciences research. Brought together here at "The Park" is a diverse collection of outstanding talent, dedicated to the task of unravelling the mysteries of environmental impacts upon biological systems, so that we may all live more congenially in the air and soil and sea around us. The difficulty of the task is exceeded only by its importance. Ours is a job that will never be completed--but that is part of its fascination.

I view this Institute and its focus on the environmental health sciences as a symbol of the rounding out of the biomedical research armamentarium of the NIH. This concept was summarized by my predecessor Donald S. Fredrickson who told a congressional committee some years ago that there are three great generic categories of inquiry in biomedical science. One, he said, is to understand biological systems. Another is to understand how the genetic code determines the fitness of individuals in regard to the functioning of their biological systems. The third, Fredrickson said,

> . . .is a question of how man and other animals adapt to the environment and ecology in which they live, and that adaptation is dependent both on the nature of the environment and on the genetic structure. . . .(1)

All three categories of inquiry are now being vigorously pursued by the National Institutes of Health. While the work of all 11 of our Institutes is a collaborative effort that intermingles at many levels, it is the specific charge of NIEHS to link the biological processes with the world around us. The study of the interaction is a huge task, and a vital one, if we are progressively to break down the barriers to prevention and cure of the chronic and degenerative illnesses that presently seem so formidable.

This Institute draws upon the knowledge base of NIH as a whole in pursuing its mission. In that sense, it exemplifies the broad reach of the entire agency. It conducts and supports research to develop new knowledge germane to the processes by which human health can be adversely affected by the environment. This involves a broad spectrum of disciplines and approaches, ranging from basic studies of molecular and cell biology to research associated with the detection of hazardous chemicals, and with the extrapolation of laboratory data to man, and the estimation of risks of human exposure.

For example, through his chairmanship of the National Toxicology Program, Dr. Rall leads a Departmental effort to strengthen the science base in toxicology, to test potentially toxic chemicals, and to develop more sensitive and rapid methods for testing toxicity. The program helps to avoid duplication of effort and provides a vehicle for setting priorities among chemicals of concern. The information developed through NIEHS is essential in designing effective disease prevention strategies. This Institute has identified prevention of environmentally related deseases as a major priority. In this fiscal year (1983), for example, the Institute expects to devote approximately 90 percent of its budget to activities considered disease prevention.

The mechanisms by which environmental agents contribute to chronic and degenerative diseases remain poorly understood. Nevertheless, there is no question that the environment--man-made and natural--is a major factor in disease and disability. I am personally persuaded that the relationship is

greater than has heretofore been appreciated. Recent findings point increasingly toward the causal importance of dietary, occupational, industrial, and other environmental factors in several of the major diseases of today. Many of these factors result from activities that are subject to human control. Many are byproducts of modern technology and, therefore, require continuous balancing of social benefits against health risks by policy makers in our government. We cannot achieve a zero-risk society, but it is appropriate that the people themselves, through their elected representatives, decide which risks are worth taking.

I have described NIEHS as a symbol of the broad, integrated approach to the pursuit of biomedical knowledge and the conquest of disease that is followed by NIH as a whole. There is another vital aspect of this approach that must also be emphasized; that is, the larger community of effort that translates new knowledge into medical practice and measures for health maintenance.

The makeup of this larger scientific research community underscores the fact that there is no Federal monopoly on health research. We include in the research community, laboratories at publicly supported and private colleges, universities, academic health centers and teaching hospitals, the laboratories of industry and the work supported by voluntary organizations and foundations. The breadth of NIH programs is indicated by the fact that well over four-fifths of NIH expenditures support extramural biomedical research in universities, private laboratories, and elsewhere. While the NIH campus in Bethesda (and its extension here) is the largest single biomedical research

institution in the world, our intramural research programs account for only about one out of every $25 spent on such work in the United States.

The support of basic research is a responsiblity of Government, for the dual reasons that it benefits the people and the economy of the nation and that there is no other substantial source for its support. The bulk of support for basic biomedical research, conducted mainly in university laboratories, will continue to come from the Federal Government, primarily through NIH. In 1981, for example, 78 percent of health R&D funds used by universities came from the Federal Government; 19 percent from university, state, local, and other non-profit sources; and 3 percent from industry. While industry has an important role in the continuum of health science research, its emphasis is chiefly on development and application. The primary search for basic knowledge will continue to be conducted by universities and Federal laboratories, with Federal dollars.

We are now entering the fifth decade of the Federal-academic partnership in biomedical research. We can take a degree of encouragement in making predictions for the 1980s from the fact that the principles shaping that partnership have changed little since the years immediately after World War II. A number of issues we face in the 1980s were foreseen in the 1940s--for example, what to do about obsolescent equipment and instrumentation, patents, indirect costs, rising direct costs, and small business involvement. The Federal approach to support of health research through universities has served the national interest well through the years. The basic concept of the Federal-academic partnership was expressed in a 1945

report entitled, "Science--The Endless Frontier," written by Dr. Vannevar Bush, the President's Science Advisor. The flavor and substance of the document stand up well when viewed from the perspective of nearly 40 years. Permit me to read a few sentences from it:

> The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. . . . Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences.(2)

Such "discoveries in remote and unexpected fields" are the objective of the Government-university partnership. A concept expressed in the 1920s by Alfred North Whitehead characterizes our present effort. Whitehead said: "The proper function of a university is the imaginative acquisition of knowledge." I like to think that this concept can be applied to the function of NIH as well.(3)

An isolated fact is interesting but not useful until imagination places it in a larger context. At that point, as Whitehead said in the same lecture, "a fact is no longer a bare fact: it is invested with all its possibilities." To be engaged in "the imaginative acquisition of knowledge" at this time is, in my opinion, the most exciting opportunity in the history of health science research. The recent flood of advances in biomedical research has justifiably led to the use of the phrase "biological revolution" to describe the present state of the life sciences. This surge of new knowledge, the result of more than three decades of vigorous public support of biomedical research, has produced outstanding opportunities for progress and

has created an unprecedented potential for the application of this knowledge to the improvement of health. The barriers are coming down; biomedical science has probed the innermost secrets of living processes at the cellular and molecular levels. Let me mention just a few of these areas of high promise to be pursued in the immediate future:

--First, the development of recombinant DNA technology has given us an exciting tool that allows us to transfer hereditary units from one species to another and permits bacteria to become factories for the production of substances of biological, agricultural, and medical importance. The use of this technique has already led to the synthetic production of human insulin, somatostatin, and growth hormone. Recombinant DNA technology also can be used to produce large quantities of pure antigen which, in turn, can be used as vaccines for immunization against infectious agents.

--Second, the development of hybridoma cell fusion technology has led to facile production of an array of monoclonal antibodies for use in exquisitely specific vaccines, diagnostic tests, and treatment for many diseases. Recently, investigators have used human lung cancer cells to prepare monoclonal antibodies that can distinguish tumor cells from normal cells. This technology may permit the detection of cancer at a very early stage. In a few instances, clinicians have been able to attach radioactive or chemotherapeutic agents to the antibodies and thereby kill cancer cells without harming surrounding healthy tissue.

--Third, the past decade has seen rapid growth in our knowledge of neurobiology; we are achieving a progressively better understanding of the function of the brain and central nervous system in health and disease. The discovery of slow viruses that cause significant neurological damage has been a major advance. Methods of opening the blood-brain barrier selectively have been identified and are being investigated to allow enzyme replacement in certain genetic diseases. Progress in microsurgery has greatly improved the outlook for patients with certain neurological conditions, including brain tumors and acoustic neuroma. New diagnostic tools, including computerized axial tomography (CAT), positron emission transaxial tomography (PETT) and, most recently, nuclear magnetic resonance (NMR), allow detailed imaging of the living human brain and its functions and promise to uncover a wealth of knowledge. Work on neurotransmitters, such as L-Dopa, and neuropeptids, such as encephalins, has greatly expanded our knowledge of communication within the central nervous system. I agree with many scientists who believe that neurobiology is the frontier science of this decade.

--Fourth, a major concept of cancer causation, introduced in the 1960s, continues to gain support from new sero-epidemiological evidence. This is the concept of <u>oncogenes</u>--genes that cause tumors. Like other genes, these serve as templates for DNA that direct the production of enzymes that, in turn, catalyze the synthesis or modification of proteins. The protein products have been called oncogenic proteins, since their action causes neoplastic transformation of cells. "Onc" genes have been detected in a wide variety of vertebrate species, including man. The oncogene

concept suggests that in the course of evolution an RNA-type virus became incorporated in the germline, or genome, and exists there as a silent infection before birth. It is proposed that these genes can be activated by a myriad of environmental agents that then serve as proximate causes of cancer.

Scientific advances such as these form the deepening foundation upon which we will build important achievements and health benefits in the years ahead. They will not come quickly or easily, but there is a momentum to science that will not be denied. There is much to do. We still do not understand the fundamental processes and mechanisms of heart disease, cancer, stroke, schizophrenia, arthritis, diabetes, and other major diseases. We must set our priorities in full awareness of the enormous toll of such disorders, but also with a realistic assessment of the existing state of knowledge and the readiness for discovery in each field.

The rate of progress in the ceaseless war on disease is a function of scientific opportunity, which we now have in abundance, the imaginative insight of scientists, and available funds. We are simultaneously involved in the adventure of discovery for its own sake and in pursuit of better health for all. What a combination: satisfying work in a great humanitarian cause.

But how shall we make sure that the momentum of scientific discovery is continued? We have entered a period of financial constraint in biomedical science. The period of explosive growth of support for biomedical research of

science. The period of explosive growth of support for biomedical research of the fifties and sixties, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. The second stage rocket of the Cancer, Heart Disease and Stroke initiative has now played out. After reaching an all-time high in constant dollars in 1979, the NIH budget has leveled off, and has in the past three years declined about 12 percent in the same dollars. The NIH is now a mature agency competing with other Federal programs for its share of the budget. In the context of the present economy NIH has been well treated by the Administration and the Congress, but it cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new steady state that, all of us, NIH and universities alike, would do well to view as the future norm. A number of painful adjustments will be necessary if we are to secure the greatest amount of the best science within our available resources. Since it may not be possible to continue all the efforts and programs we have come so passionately to cherish, we will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration. Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of

fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period. Incidentally, in fiscal year 1982, which ended on September 30, we managed to fund 5030 such new and competing renewal awards.

Finally, the third element of these timeless principles is that there is a continuing need to assure a supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between the continued productivity of research and the availability and replenishment of the supply of qualified investigators.

Beyond those statements of principles are certain other responsibilities that also must be considered by NIH. We must recognize a need for balance between the fundamental pursuits and other NIH program components in order to assure uninterrupted progress in all segments. Among those additional components are the following six illustrations:

--Research centers which conduct multidisciplinary research focused on specific health problems, intergrate basic research with clinical application, and provide a vehicle for transferring new scientific knowledge into practice in community health care settings.

--Research resources to strengthen, enhance, and maintain the quality of the environment in which biomedical research is performed.

--Biomedical communications involving the acquisition, storage, and dissemination of information needed in research, health professional education, and the delivery of health care services.

--International research activities to facilitate the exchange of scientific information and promote collaborative research efforts.

--Clinical trials to advance knowledge concerning the prevention, diagnosis, and treatment of disease and to provide evidence of safety and efficacy of new therapy.

--Special emphasis on the prevention of disease and the promotion of health as part of a Department-wide initiative.

These, then, are the major responsibilities of NIH which must be weighed in establishing our priorities and programs for the future. But the underlying principles on which all of our work is built remain the pursuit of

basic research, support of independent investigators and their ideas, and the training of future scientists.

Closer to home, here at NIEHS, major programmatic efforts illustrate the broad nature of modern biomedical inquiry--genetic toxicology, reproductive and developmental toxicology, and health-risk estimation. These areas all involve research under way in other Institutes as well.

More specifically as regards NIEHS:

--This afternoon you will hear of a study to be made of environmental factors possibly involved in renal failure. These agents include lead, cadmium, analgesics, and solvents. What, if any, is the connection with renal failure? What are its dimensions? And by what processes might it lead to pathology? You will also be told of investigations into asbestos-induced lung disease and effects of certain chemicals on the male reproductive system. Merely naming these topics of inquiry indicates the wide-ranging potential effects of environmental substances on various organ systems and the broad scope of studies on the NIEHS agenda.

--Raised levels of aluminum and zinc have been associated with dementias that occasionally occur during the course of chronic renal dialysis. A possible role of aluminum has also been proposed in chronic dementia of the Alzheimer's type, but this hypothesis has prompted considerable controversy. Scientists supported by NIEHS have now confirmed findings of raised aluminum in the brain of Alzheimer's disease patients, and have

devised a means to pinpoint the site of aluminum concentrations in the hippocampus of the brain. The question of the etiological role of aluminum, if any, remains open, but the investigation continues.

--A final instance that I would like to cite concerns unexpected findings made by NIEHS scientists who were investigating effects of the estrogen DES on children of mothers who used this hormone during pregnancy. In experimental studies in rats given DES, they discovered abnormal development of genitalia in male offspring. Subsequently, other scientists reported findings that male offspring of DES rat "mothers" were sterile. This outcome has since also been observed in clinical practice.

These are illustrations of the sometimes surprising findings that prompt further study and, thereby, lead us closer to the answers we seek. The prospects are clearly for greater-than-ever achievement in the future; the record of the past gives us reason for confidence.

Finally, I want to emphasize what I consider to be a heartening omen in an era of economic slowdown, and that is the strong support for biomedical science from both the President and the Congress. The Administration expressed its continued strong support for biomedical research in the President's budget request for this fiscal year--an increase of $109 million, from $3.64 billion in 1982 to $3.75 billion in this fiscal year--at a time when other health allocations are being curtailed. As many of you know, the

House Appropriations Committee has approved a bill that would provide slightly more than $4 billion for NIH this year. The Senate markup of its bill is only slightly less. Whatever the final outcome on our budget, we will strive to maintain the highest level of support possible for new and competing research project grants and for the continuing years of multi-year project awards.

I believe that the strong and healthy partnership of NIH and the universities of this country, based on long-standing principles of cooperation in the cause of science, will serve us well in arriving at mutually agreeable and productive solutions to the problems we face.

As we confront the issues of the 1980s and beyond, we must renew our commitment in support of the overriding objectives we share--the conquest of disease and better health for all. Through our joint pursuit of the "imaginative acquisition of knowledge," I am confident that we will continue to move steadily toward realization of our goals.

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CENTENNIAL SEMINAR*

by

James B. Wyngaarden, M.D.**

As we begin, I would like to thank you, Dr. Schwartz, for inviting me to participate in the Centennial celebration of the University of Colorado School of Medicine. Your 100th anniversary makes you twice as old as Duke University Medical Center, the institution I was privileged to serve for twenty-five years and which has made a number of outstanding contributions to your faculty. As a matter of fact, in preparing for this talk I was tempted to emulate Charles Scoggins, and quickly to show two slides of NIH mechanisms and then abruptly to switch to some lighter topic such as "Molecular Biologists of the Old West," but since they were probably just as shady as "Doctors of the Old West"--a favorite Scoggins theme--I decided to stick with my original subject--"The future of biomedical research." However, I must confess that I have become increasingly uncomfortable with that title. When Dean Schwarz called to invite me to speak today, I was flattered and pleased. I quickly checked my calendar and found a little daylight in the first week of December. A few weeks later there came an urgent request for a title. I did what most speakers do when harassed by sensory overload and when required to think momentarily about an event

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far in the future: they choose a somewhat grand and utterly nondescript title that will permit them to say whatever is on their minds when that future date arrives. I now recoil a bit at the sweep and ambition, perhaps even the presumption, of the title. A more appropriate description would be "Some personal and fallible thoughts on the future of biomedical research."

I am, of course, aware that this invitation has come to me as the relatively new Director of the National Institutes of Health. I have now been in my position about eight months. It has been a time of extraordinary learning for me. One of the first things I learned was that I had to be careful in suggesting that something be done, because there was a high probability that someone would do it. I never had that problem at Duke. One of the early surprises was the intensity of the interactions between NIH and a multitude of special interest groups and their Washington representatives, as well as with the Members of Congress. I was astonished to learn that sometimes Congressmen make deals in order to gain support for their pet projects, and also that the Administration sometimes abruptly changes its mind under interesting circumstances. I wasn't aware of that before. I now understand what is meant by the saying that there are two things you do not want to know how they are made. One is sausage and the other is legislation.

But irrespective of the process, many of the laws passed by Congress turn out to be wise, even visionary, and of enormous benefit to the American people. I place the succession of laws that established and molded the NIH in that category. The

origins of the NIH go back to the Laboratory of Hygiene, established in 1887 as a component of the Public Health Service on Staten Island. Thus, we too are approaching our one hundredth anniversary. The Laboratory was later moved to Washington and, in 1930, was named the National Institute of Health. In 1937, the National Cancer Institute was established as a separate and coordinate entity. But prior to World War II the role of the American government in medical education and in biomedical research was minimal. Private foundations, voluntary organizations, and the professional societies were the dominant sources of support and influence in shaping medical education, funding research, and carrying out health promotion programs. When, out of the wartime experience, it was recognized that federal support of research was not only appropriate but essential, agencies like NIH were provided comparatively massive support. The Public Health Service Act of 1944 established the legislative basis for future developments. The National Institute of Health and the National Cancer Institute were merged. An order of the Surgeon General in 1947 established the Experimental Biology and Medicine Institute. In 1948, Congress created the National Heart Institute, the National Institute of Dental Research, and the National Microbiological Institute. The new agency was named the National Institutes of Health. In the succeeding years several other Institutes, Bureaus, and Divisions were added so that we now have sixteen operating units, and incidentally sixteen separate budgets to be negotiated with the Administration and the Congress each year.

My personal association with the NIH goes back to 1951, when I joined the National Heart Institute in a position that, as far as I knew, had no name, but would now be called a clinical associate or clinical staff fellow. Dr. James A. Shannon was at that time Associate Director in Charge of Research in the Heart Institute. When he became Director of the NIH in 1955, the budget of the entire NIH was $82 million. When he retired as Director, thirteen years later, the NIH budget had passed $1 billion. During Dr. Shannon's tenure, the basic mechanisms of support of biomedical science were established and these have continued to serve us well. Jim Shannon insisted that congressional mandates to conduct research in cancer, heart disease, and arthritis, for example, be interpreted broadly. He realized that the science base did not exist to permit a frontal assault on the diseases themselves. He set about to build the research capability of this country, both through the intramural program at the NIH in Bethesda and through a substantial expansion of the mechanism of grants-in-aid to institutions. Corollary objectives included the strengthening of the institutions in which biomedical research would be done, and the development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and the brightest young minds resident in the universities. Together with Hill-Burton money for clinical facilities, NIH construction funds for research facilities modified the topography of the academic medical center, and indirectly changed, and most of us would say greatly strengthened, medical education.

NIH has proceeded on a course that, in many ways, was charted by a report written by Vannevar Bush, the President's Science Advisor, in 1945, which greatly influenced Congressional action in the immediately succeeding years. This report, entitled Science--The Endless Frontier, outlined policies for Federal support of health research that have served the national interests so well since that time. The flavor and substance of the document stand up in sturdy perspective when viewed with the critical hindsight of nearly forty years. I would like to read a few sentences from it:

> "The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge . . ."[1]
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> "While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any extension of medical facilities must be accompanied by an expansion of medical training and research.
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> "Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."[2]

Permit me to leap forty years beyond Bush, and to quote our current President's Science Advisor, Dr. George Keyworth. In a recent speech he stated, "Basic research warrants government

support because it is an investment in the future--in a better quality of life, better security, a better economy, and simply better understanding."[3] In the same speech he also emphasized that basic research was a responsibility of government for the dual reasons that it benefited the people and the economy, and that there was no other source of support for basic research on the scale required.

Support of biomedical science during the past three decades, chiefly by the NIH, has transformed our knowledge and understanding of biology. The transformation has been so dramatic, so pervasive, that it justifies the use of the overworked term "revolution." Never in the history of biological science has there been so much exciting work going on, so many exquisitely promising leads in so many fields, or such an army of brilliant scientists at work in their laboratories or at their blackboards. Molecular biology, which had its beginnings in the 1950s as an exhilarating intellectual adventure in bacterial genetics with no predictable public benefit, has through recombinant DNA technology permeated all branches of biological science. We now have human insulin being produced by bacteria. In India, agricultural scientists are now exploring how nitrogen fixation genes can be insinuated into wheat and rice. The discovery of oncogenes has provided a new paradigm for cancer research. In immunology the once obscure flocculations and precipitations of test-tube scientists have now given us a wholly new insight into a range of human diseases, and in the instance of monoclonal antibodies have provided us a tool whose power is yet to be fully

exploited in terms of targeted chemotherapy, and even fertility control. These are impressive examples of the social utility of basic science, and also of the patience needed for the practical development of beneficial measures based upon discovery of new fundamental knowledge.

"Discoveries in remote and unexpected fields" are the objective of the Government-university partnership. A concept expressed in the 1920s by Alfred North Whitehead characterizes our present effort. Whitehead said: "The proper function of a university is the imaginative acquisition of knowledge." I like to think that this concept can be applied to the function of NIH as well.[4]

An isolated fact is interesting but not useful until imagination places it in a larger context. At that point, as Whitehead said in the same lecture, "a fact is no longer a bare fact: it is invested with all its possibilities."[5] To be engaged in "the imaginative acquisition of knowledge" at this time is, in my opinion, the most exciting opportunity in the history of health science research.

But how shall we make sure that the momentum of scientific discovery is maintained? We have entered a phase of financial constraint in biomedical science. The period of explosive growth of support for biomedical research of the fifties and sixties, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. The second-stage rocket of the Cancer, Heart Disease, and Stroke initiative has now played out. After

reaching an all-time high in constant dollars in 1979, the NIH budget has leveled off, and has in the past three years declined about 12 percent in the same dollars. The NIH is now a mature agency competing with other Federal programs for its share of the budget. In the context of the present economy NIH has been well treated by the Administration and the Congress, but it cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new steady state that all of us, NIH and universities alike, would do well to view as the future norm. A number of painful adjustments will be necessary if we are to secure the greatest amount of the best science within our available resources. Since it may not be possible to continue all the efforts and programs we have come so passionately to cherish, we will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration. Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term

advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period.

The third principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between the research productivity and the availability and replenishment of the supply of qualified investigators.

How well is the enterprise working, and what can be foretold of the future? What are the stresses on the system? What are the immediate concerns and the long-term problems?

I mentioned earlier that the support of basic research is a responsibility of Government. This tenet has been explicitly reaffirmed by the Reagan Administration. In the case of basic biomedical research, which is conducted mainly in university laboratories, the bulk of support will continue to come from the Federal Government, primarily through NIH. In 1981, for example, 78 percent of health R&D funds used by universities came from the

Federal Government; 19 percent from university, state, local, and other nonprofit sources; and only 3 percent from industry. While industry has an important role in the continuum of health science research, its emphasis is chiefly on development and application. The primary search for basic knowledge will continue to be conducted by universities and national laboratories, with Federal dollars.

During most of the history of the NIH, certainly for the past 10-15 years, about four-fifths of the agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. A large portion of that support goes to academic health centers such as this one at the University of Colorado for the compelling reason that you have a national resource for which there is no substitute--your faculties of trained basic and clinical scientists. And further, one of your central purposes is to ensure the continuing renewal of that precious resource--the trained investigator.

I also mentioned earlier that in my judgment the budget for biomedical research, more specifically the budget of NIH, could not be expected to grow substantially in constant dollars in the immediate future. But it is a very large budget, about $3.6 billion in FY 1982, and tending toward $3.9 or even $4.0 billion in FY 1983. The difficulty is that existing commitments against that budget, resulting from award decisions made in previous years, have restricted flexibility in making new awards, and have forced NIH to examine and to order its priorities much more carefully than during its two great periods of growth, which I have

described as the Shannon era of 1955-1968, and the Cancer, Heart Disease, and Stroke period of 1971-1979. The constraints of budget have led to a policy of stabilization under which investigator-initiated research projects and research training have been given top priorities. In order to stabilize essential research programs, and to reduce the turbulence of the system, NIH has endeavored to fund a minimum of 5,000 new and competing renewal awards each year, and to support a minimum of 10,000 trainees each year. I would like to address the matter of research grants first, and defer until a little later any further reference to training.

NIH succeeded in funding about 5,100 new and competing awards in FY 1981, and 5,030 such awards in FY 1982 which ended on September 30. The latter number is almost 300 awards greater than the predicted figure of 4,741. The increase was achieved by budgetary shifts (about which more will be said in a moment), downward negotiation of the size of awards, and the assignment of virtually all year-end dollars recaptured from unexpended awards of whatever category to the funding of new research grants. During both FY 1981 and FY 1982, 50 percent of our budget went into the support of investigator-initiated grants. This represents an increase from 39 percent of the budget only a few years earlier.

The stabilization policy makes a powerful statement to the extramural community. It says that NIH is doing its utmost, consistent with program balance and congressional mandates and directives, to assure that the best research will be adequately

funded, and that young scientists will have opportunities in research, that we will protect their entry into the research enterprise--not out of charity but because the vitality of the enterprise, the success of the research endeavor, depends on them. In both 1981 and 1982, 50 percent of all new research grant awards went to principal investigators who were first-time applicants. This number represents 12 percent of our total portfolio of about 16,000 grants.

But the stabilization policy also has its down side. In order to fund 5,000 new and competing projects, dollars have been shifted from other mechanisms each year for the past 3 or 5 years. While the proportion of the NIH budget assigned to support investigator-initiated research projects has grown from 39 to 50 percent, other mechanisms have been curtailed, especially contracts, centers, and clinical trials. After several turns of the ratchet, many Institute Directors feel that further shifts would seriously limit their abilities to meet other program goals and to maintain program balance.

The President's 1983 budget for the NIH requested $108 million above the 1982 level. Because of commitments that carried forward, in the absence of other adjustments the 1983 budget would have permitted the funding of only 3,200 new and competing awards. In order to raise this number, further shifts were accepted by the Institute Directors and, in addition, NIH proposed to fund the institutional allowance on training awards at about 50 percent of customary levels, to reduce payment of noncompeting awards by an average of 4 percent, and to pay

indirect costs only to the extent of 90 percent of negotiated rates. These "savings," taken together, will permit funding of about 900 additional awards, raising the anticipated number for 1983 to 4,100.

During 1982, although we funded 5,030 new and competing awards, this figure represented only about a third of approved grants. The priority scores of those funded cut off at 160-180 in most cases. Unquestionably many strong and potentially productive and valuable research projects were excluded by the stringency of the budget. Excellent established investigators as well as well-qualified newcomers were denied support.

One of our critics has described the current situation as the Matthew 25:29 phenomenon: "For unto everyone that hath shall be given, and he shall have abundance: but from him that hath not shall be taken away even that which he hath."

The anxiety in the research community has led to varied responses, in my view largely constructive. In public testimony and private correspondence they have impressed upon the Congress the need for additional funds for biomedical research. Both the House and Senate appropriations committees have added funds to support a total of 4,900-5,000 new and competing awards. These bills have yet to reach the floors of the two chambers, but the portents are encouraging. But not all responses have been constructive and some, though as yet quantitatively minor, bode ill for the future if they should become common practice. Let me cite two examples. A few investigators are sending their new

grant applications simultaneously to the NIH and to their Congressmen and Senators. In one instance, we received a congressional inquiry as to why an obviously meritorious and important research project had not been funded, only to learn that the Congressman had received his copy of the application before we did. A second example involves a new category of awards that we have termed "disapproved, but funded." We now have several examples of grant applications that have been funded by specific congressional mandate after they had received too low a priority to be funded, or had been disapproved altogether.

Some scientists have attacked the fundamental integrity and equity of the peer review system. It is a human system and no one would contend that its judgments are flawless. It has operated with very little criticism for thirty years. There always has been a cutoff point below which grants could not be paid due to limitation of funds. At present some Institutes are unable to fund grants with priority scores above 160-180. Applications given priority scores just beyond the cutoff are frequently of considerable merit and we wish we could fund them. But there has always been a cutoff somewhere. However, the quality of applications at the margin differs considerably when the payline is 160 rather than 260, and the unrest in the extramural community is correspondingly higher. The only way to avoid the problem altogether is to be able to pay all approved grants, and this utopian day is unlikely ever to arrive. Applicants whose priority scores fall outside the payline are provided information on the shortcomings of the application and have the

option of rewriting their material and resubmitting. In the last round of grants reviewed by the NIH, 23 percent of all grant applications received were resubmissions. There is also an appeal mechanism for any applicant who feels that he or she has not been dealt with fairly.

Others have suggested a limitation of the dollar support awarded to any individual principal investigator. This proposal has taken several forms. One is to limit the number of dollars per project or per laboratory. Another is to limit the number of grants in the name of any principal investigator. At present about 10 percent of principal investigators have two or more grants, although frequently the second is a training grant or salary award. Since the NIH supports projects, we are only permitted to ask regarding additional support available for the project under review. Thus our information on the total financial support of any principal investigator or laboratory is incomplete and without such information, we would have difficulty in dealing equitably with either of these two proposed mechanisms. A third proposed mechanism which has received far greater support is that of a sliding scale in the payment of approved awards. It is suggested that NIH should fund grants of the very highest priority scores at 100 percent of the award rate, the next category at 90 percent, followed by 80 percent, 70 percent, and so on. We have examined this concept very carefully but find it flawed in several particulars. At present, the recommended level of support of grants approved by study section averages 18-20 percent less than the requested amount. The actual award rate

is further negotiated by the extramural grants management division, and currently averages about 8 percent below the rate recommended by the study section. The severity of downward negotiations both by study sections and grants management specialists roughly parallels the priority score. In other words, those grants with the highest priorities tend to be paid in amounts closer to the requested budget than those with somewhat lower scores. Thus there are within present practices some features of the sliding scale philosophy. But we are reluctant to formalize the sliding scale mechanism or to apply it mechanistically. In our view, such a practice would fund many projects inadequately and would result in waste of taxpayers' money. It would reduce the average cost per project, and since this is one of the factors in the construction of budget requests to Congress, such a change would have the self-defeating consequence of reducing subsequent NIH budgets and of making it possible for us to fund even fewer grant awards. As we have reviewed these alternatives for spreading research dollars across a larger number of investigators, we have reaffirmed the traditional practice of awarding grants on the dual bases of scientific merit and program relevance, as determined by study section and council review. Some years ago Philip Handler, former President of the National Academy of Sciences, stated in congressional testimony: "In science the best is vastly more important than the next best."[6] Jay Keyworth, the President's Science Advisor, has characterized science as "an unabashed meritocracy."[7] John Gardner, in his book on Excellence, asks: "Can we be excellent and equal

too?"[8] While we share a deep concern for scientists whose deserving projects we cannot fund, we think that the interests of science are best served by funding the most meritorious work as judged by the peer review system, and by assuring that such projects are funded parsimoniously yet adequately for the execution of the study.

A second major arena of vigorous response to the President's 1983 budget has been the proposal to pay only 90 percent of the negotiated rate of indirect costs on NIH research grants. Let me define the problem as it is seen by the NIH. Prior to 1966, the NIH paid a flat rate of 15 percent of the total award to cover indirect costs of a project. The Wooldridge Report of 1966 recommended that NIH abandon the flat rate, and instead pay a negotiated rate of indirect costs based on audits.[9] For the next six years the average indirect cost rate rose rapidly, and by 1972 amounted to 24.2 percent of the total research dollar. Since that time it has risen less sharply but at a steady rate of 0.53 percent per year. In FY 1982 it reached 30.0 percent of the total grant dollar.

This inexorable rise of the total fraction of the research budget represented by indirect costs has occurred irrespective of the rate of change of the research budget itself.. The linear increase is the same during the expansion of the NIH budget resulting from the Cancer, Heart Disease, and Stroke initiatives as during the constriction of the budget since 1979. In FY 1982, the budget of the NIH for awards and contracts increased $52 million. Of this, $29.1 million, or 56 percent, was consumed by

indirect costs. In virtually every one of the last 16 years, the indirect cost rate has grown faster than the direct cost rate. The issue has been raised to a high level of visibility by the responses of university administrators to the Congress. The administrators are understandably concerned about the solvency of their institutions, and emphasize that indirect costs are true costs of research, a point we do not contest. In the current continuing resolution Congress has temporarily provided additional funds for full payment of indirect costs. However, Congress is also concerned about the rte of growth of indirect costs. In its report on the proposed 1983 budget, the House Committee on Appropriations has asked for two studies of indirect costs, one by the Department of Health and Human Services, another by the Government Accounting Office. At issue is the containment of indirect costs, and the extent of cost sharing between the universities and the Federal Government. This has become a divisive issue which requires early resolution. The present proposal of paying only 90 percent of negotiated rates has an unfortunate consequence of penalizing those schools that have kept indirect costs low and well as those that have not. Such a proposal is clearly not a long-term solution, and indeed it was proposed only as an interim device. I anticipate that a satisfactory resolution of this matter will be developed within the next year.

To this point I have outlined the fundamentals of our approach to the support of medical research by NIH, and the current policy of stabilization which gives top priority to

investigator-initiated research projects. I would now like to raise a subject of special concern, namely the present and future state of clinical research. A burgeoning of basic knowledge in the past decade has opened up vast opportunities for clinical research. Nevertheless, a diminishing share of physicians are interested in applying themselves to the clinical research needs of tomorrow. Some quantitative data may serve to emphasize the points to be made. Figure 1 shows the number of principal investigators on all research project grants holding M.D., Ph.D., or combined M.D. and Ph.D. degrees, as these have varied during the past dozen years. Notice the decline in the number of M.D. investigators holding such awards from about 3,400 in 1968 to about 2,500 in 1973. Since that time the number has increased slightly but in 1980 was still below 3,000. The number of Ph.D. principal investigators has always been somewhat greater than of M.D. investigators. It declined slightly from 1968 to 1973, but since that time has displayed an almost linear growth. When these data are expressed as a percentage of all principal investigators on research grant awards, as in Figure 2, they describe a rather steady decline in the percentage of grants held by M.D. principal investigators from about 35 percent of the total in 1968 to about 23 percent in 1980.

During the same time span the percentage of grants held by Ph.D. principal investigators increased from 52 to 67 percent. The percentage held by M.D.-Ph.D. principal investigators has remained nearly steady at about 10 percent of the total. The decline in the number and percentage of M.D. investigators

reflects to a large extent the submission of fewer grant applications by M.D. than Ph.D. scientists. The approval and award rates for competing research grant applications did not differ greatly for M.D. and Ph.D. applicants between 1974 and 1980.

Figure 3 shows a table of such rates for all competing awards, both new and renewal applications. The approval rate for applications submitted by Ph.D. investigators has run 4 or 5 percentage points ahead of rates for M.D. investigators. But of the grants approved by study sections, the award rates for M.D. and Ph.D. principal investigators have been virtually the same.

When one looks at the success of new applicants alone (Figure 4), one finds that there has been a divergence since about 1974, with new M.D. applicants competing somewhat less well than new Ph.D. applicants, and with both groups competing less successfully than the M.D.-Ph.D. applicant. This trend is even more dramatic when expressed in comparison with the average success rate of all research grant applications of that year, which in Figure 5 has been given a score of 1.0. Note that increasingly the greatest success is obtained by the M.D.-Ph.D. applicant, followed by the Ph.D. applicant at somewhat above the average rate, and by the M.D. applicant who is increasingly below the average rate. The disparity of success rates of M.D. applicants is even more impressive in the subfraction of M.D.-authored grant applications that constitute clinical research in its most specific form, namely research that requires the doctor-patient relationship in its performance. Figure 6 tabulates the

shortcomings of poorly rated or disapproved NIH grant applications. The data presented apply to the entire spectrum of grant applications. An analysis of the reasons why grants submitted by M.D.s fail, and in particular why those involving clinical research fail, shows that the shortcomings follow the same profile of causes as those of the pool in general. Most such grants fail because of a faulty hypothesis, or of some flaw in experimental design, most commonly in technical methodology. Rejections because of inadequacy of investigator are no more frequent in the case of M.D. investigators than for the entire pool.

In his Presidential Address to the Association for American Physicians in May 1982, John Oates documented the correlation between the success rate of physician applicants for research support and the length of training of the applicant.[10] The success rate was poor with less than two years of postdoctoral research training; but it was even better after three or four such years than after two..

In my view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science. Clinical research requires experiences

not represented in most medical school and house staff experiences. The quality of a research grant application is a reflection of the competence and sophistication of the investigator applicant. As Damon Runyon said, "The race is not always to the swift or the battle to the strong, but that's the way to bet."

The clinical investigator provides the indispensable link between the laboratory and the human being who is the ultimate focus of all of our endeavors. For this reason we view with great concern the decline in the number of M.D.s in NIH-supported research training programs from 4,500 in 1971 to about 1,800 in 1981.

When NIH research training programs were modified in 1974, under the National Research Service Awards Act, to provide training exclusively for research or academic development, a committee of the National Academy of Sciences recommended that 2,800 clinical research training slots be offered annually, 2,400 as traineeships, and 400 as direct fellowships. This figure of 2,800 clinical training positions was not reached until 1980, but at that time 900 of these clinical traineeships were held by Ph.D. trainees, only 1,900 by M.D. trainees. The Academy committee has recommended that at least 85 percent of the traineeships in this category be filled by M.D. candidates. And so by every yardstick, we are failing to attract the number of physicians into research training perceived to be desirable by the Academy committee, and this bodes ill for the balance between M.D. and

Ph.D. investigators deemed essential for coordinated progress in basic science and clinical research.

Many reasons have been cited for the declining interest of physicians in clinical research. Most medical school curricula provide little or no laboratory experience that is representative of modern day biomedical science. The rise of specialty fields and the lengthening of postdoctoral training programs have extended the clinical training necessary for board certification. The requirements of many certification boards are rather inflexible and certainly do not encourage the potentially creative physician to enter research training. The payback provision of the National Research Service Award has acted as a deterrent for some potential traineeship applicants. Perhaps dominating the issues is that of the financial disincentives: the average gap between the previous year's residency salary and the first-year traineeship is now $4,500; differences between income possibilities in research and in procedure-oriented practices of medicine are very much larger. When the medical student's debt load at graduation is frequently $20,000 or more, the cumulative financial disincentives are a major factor in dissuading potential investigators from entering the field.

Fortunately this growing problem has received considerable attention in the Congress. Just a few weeks ago we received the Report of the House Committee on Appropriations regarding the proposed 1983 budget for the National Institutes of Health. Permit me to read a paragraph.

"The Committee shares the concerns that have been expressed by official and public witnesses about the difficulty of recruiting and retaining physicians for research careers, especially as all clinical research, involving human patients must be done by--or, at least, under the guidance and supervision of--a qualified physician. It is apparent and understandable that young physicians considering careers in health research are often dissuaded from applying for research training or research fellowships by their perception of instability in the Federal commitment to research and by their awareness that a research career represents a substantial financial sacrifice when compared with almost any form of medical practice. The Committee would like NIH to review this problem carefully and to suggest what steps might usefully be taken to increase the number of young physicians who will apply for research training and to retain those who do embark on research careers. The Committee will expect a report on this subject at next year's hearings."[11]

Even without that prodding, we have devoted considerable attention to this problem and have under consideration some major steps toward its solution. You may be sure that the preparation of this report will receive our most careful attention.

In the portion of the report preceding the statement on clinical research, the Committee explained its decision to increase the appropriation requested for all research training programs by over $18 million to provide for a total of 10,000 trainees--a level perceived by the Committee as barely large

enough to balance inevitable attrition from active participation in research.

NIH has already taken some steps to alleviate this shortage and is considering others. At the undergraduate medical student level, we have continued to give the Medical Scientist Training Program top priority in our training portfolio. This year we will support about 650 students in programs leading to combined M.D. and Ph.D. degrees. The NRSA permits short-term training of medical students for up to three months per year. This past year over 900 medical students availed themselves of such off-quarter training opportunities supported by NIH. With the exemption of the first year of NRSA support from payback obligation, the NIH can now reinstitute the post-sophomore fellowship or its equivalent, and thus provide a full year of research training within the medical school experience under an NIH fellowship or traineeship. The NIH also offers summer research fellowships at Bethesda, and during this past year about 50 medical students participated in that program.

In order to maximize the opportunities for young physicians to secure research training, the NIH has sent notices to appropriate review bodies to give M.D. applicants special consideration in the award of research fellowships, and has advised clinical research training program directors to give first priority to M.D. applicants before appointing Ph.D. trainees to the available slots. NIH is considering other measures that might restrict the number of clinical traineeships offered to Ph.D. applicants along the percentage guidelines suggested by the

National Academy of Sciences. But the disparity of stipend between residency and fellowship remains a serious problem. Within the next few weeks we will be discussing possible mechanisms for closing this financial gap, but adjustments adequate to achieve this goal will probably require congressional approval.

NIH also faces some longer term problems that must be addressed in the interest of the health and vitality of the research enterprise. When the economy improves, an increase in funding for scientific research and development is clearly indicated if we are to maintain our position of leadership in the world. This statement is just as true for other areas of science as it is for biomedical research. We also need to address the issues of obsolete equipment and the research facilities, which in the case of medical science now often represent buildings constructed 20-25 years ago.

But no one attending this centennial celebration needs to be persuaded of the importance of biomedical research to society or to the academic health center. Examples abound to document the relief from suffering that has resulted from the application of research advances. In addition, students, faculty, and others can readily appreciate how the curiosity and critical inquiry of research enhance the teaching and health care environment in an institution such as this one. The auditorium in the Clinical Center at the National Institutes of Health has a quotation engraved in the marble wall at its entrance, a quotation from its first Director, Dr. Jack Masur, for whom the auditorium is named, that beautifully captures this concept: "Hospitals with long

traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching, teaching lifts the standards of service, and service opens new avenues of investigation."

Thank you very much once again for the invitation to participate in this centennial celebration, and for your interest and attention this afternoon.

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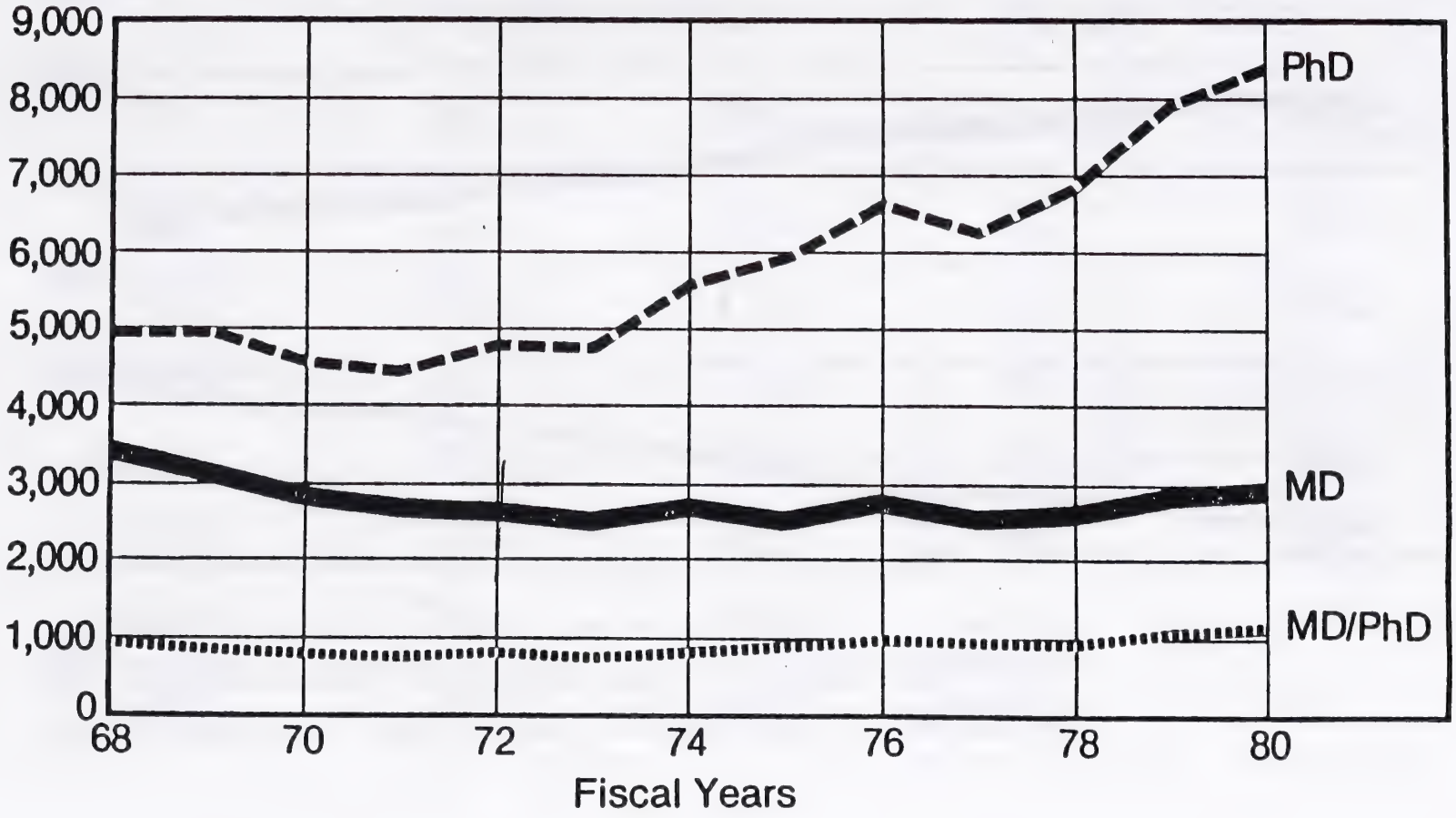
Fig 1

Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



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P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants

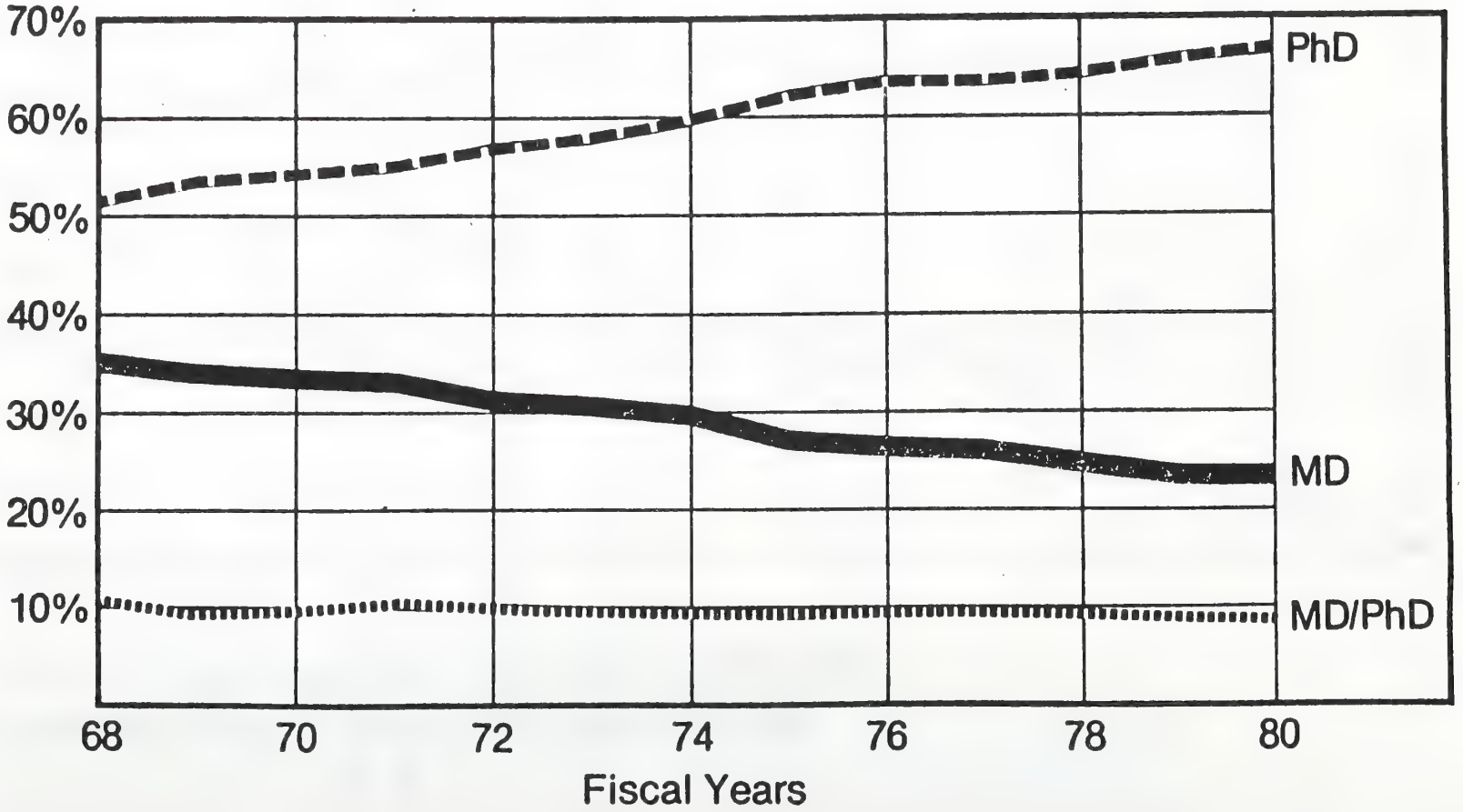


Fig 3

Approval and Awards Rates for Competing R01 Applications: 1974-1980

	Approval Rate		Award Rate	
FY	M.D.	Ph.D.	M.D.	Ph.D.
1974	73.9	78.9	60.7	56.0
1975	72.0	77.4	59.5	60.2
1976	67.7	73.8	50.4	47.2
1977	72.0	76.0	41.2	36.8
1978	74.4	80.2	44.1	45.5
1979	76.1	79.4	51.1	51.7
1980	76.7	81.0	41.5	41.7

Success of New Applicants on NIH Research Projects (Type 1 R01 Applicants by Type of Degree of P.I.)

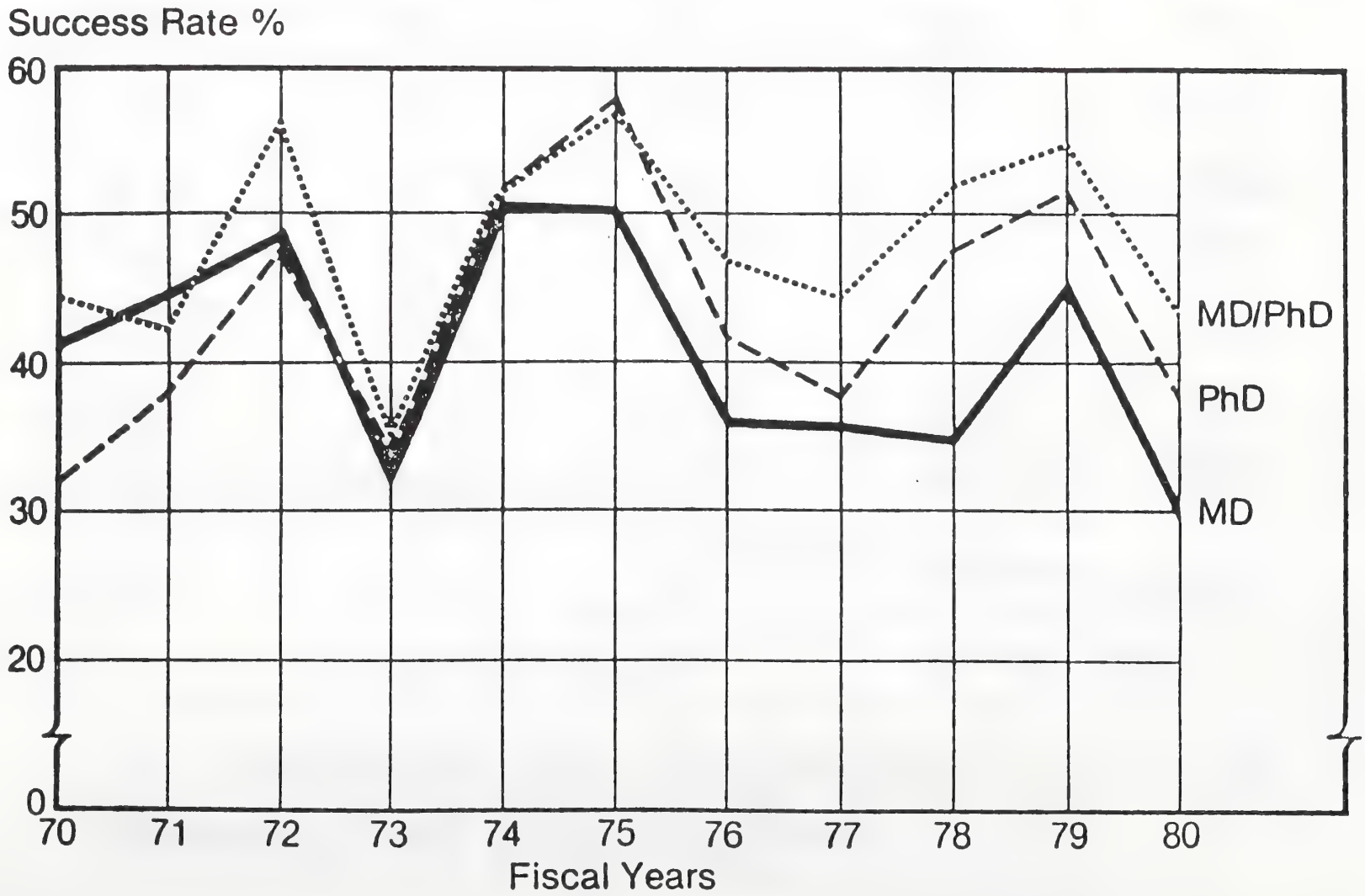
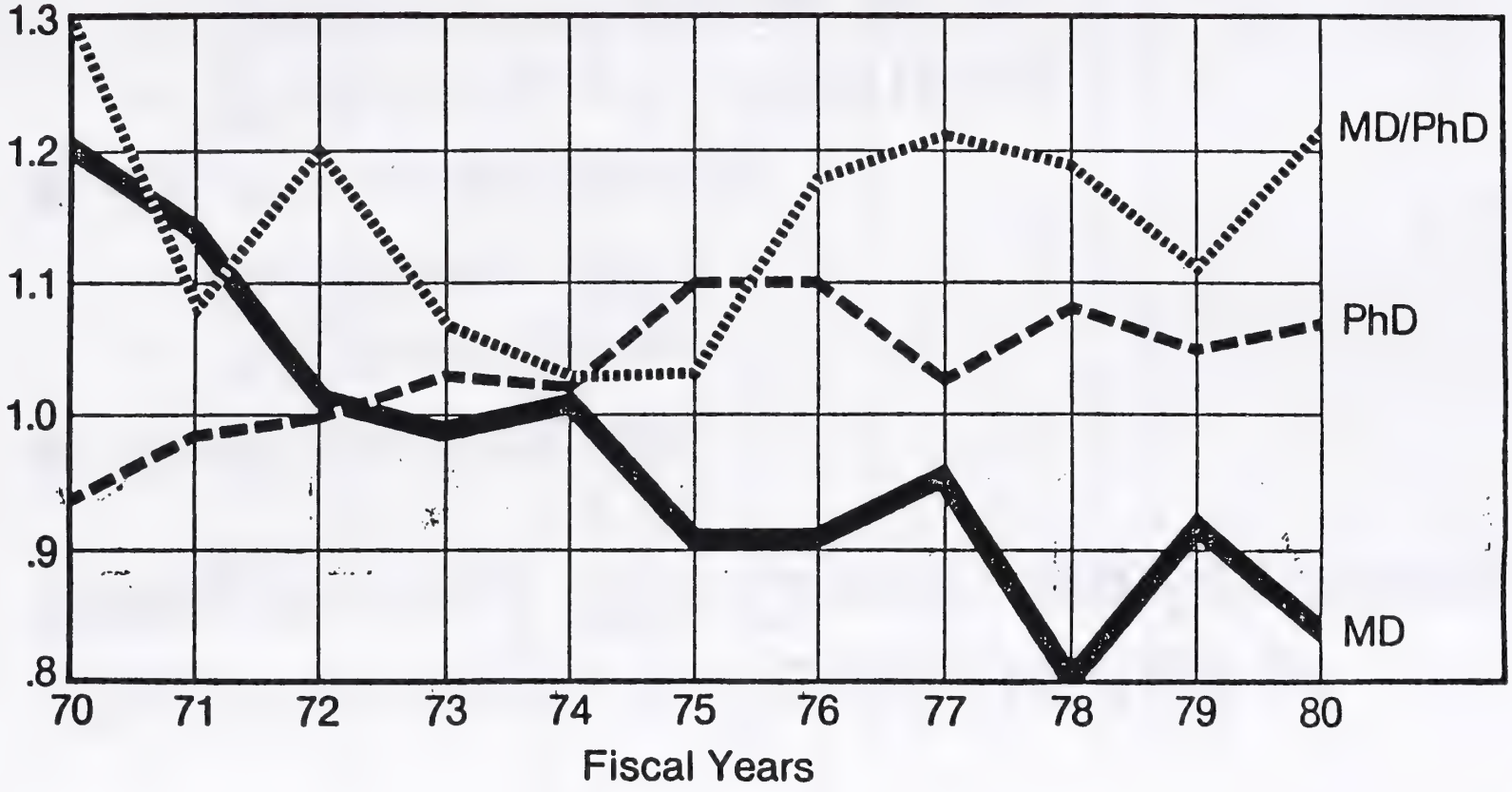


Fig 5

Success Rates of New MD, PhD and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year



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Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - Hypothesis (47%)
  - Significance (30%)
- Experimental Design:
  - Study Group or Controls (40%)
  - Technical Methodology (66%)
  - Data Collection Procedures (41%)
  - Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

EXCELLENCE*

by

James B. Wyngaarden, M.D.**

AS WE BEGIN, I WOULD LIKE TO THANK YOU, DR. SANFORD, FOR INVITING ME TO DELIVER THE INAUGURAL LECTURE OF THE GAMMA OF MARYLAND CHAPTER OF ALPHA OMEGA ALPHA, AND TO EXTEND MY HEARTY CONGRATULATIONS TO THE FOUNDERS AND ESPECIALLY TO THE NEW MEMBERS OF THE SOCIETY. THE MOTTO OF AOA, AS INDEED IT SHOULD BE OF EVERY PHYSICIAN, IS "TO BE WORTHY TO SERVE THE SUFFERING." IT WAS WITH THAT MOTTO IN MIND THAT I CHOSE AS THE SUBJECT OF MY REMARKS, "EXCELLENCE,"--FOR ELECTION TO AOA SIGNIFIES RECOGNITION OF EXCELLENCE, EXCELLENCE IN ACCOMPLISHMENTS THUS FAR, AND A PROMISE OF CONTINUED EXCELLENCE IN THE FUTURE. MEMBERSHIP IN AOA IS MORE THAN A BADGE OF HONOR. IT IMPLIES LIFE-LONG COMMITMENT TO HIGH STANDARDS. I AM CONFIDENT THAT YOU AND YOUR SUCCESSORS WILL FULFILL THIS COMMITMENT.

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*Seminar Presentation at Uniformed Services University of the Health Sciences, Bethesda, Maryland. December 8, 1982.

**Director, National Institutes of Health, Bethesda, Maryland.

IT WILL IN NO WAY DIMINISH THE HONOR WE EXTEND TO THOSE ELECTED TO AOA AS STUDENTS TO OBSERVE THAT THE FULL RECORD IS NOT WRITTEN IN THE ACADEMIC ACHIEVEMENTS OF THE MEDICAL SCHOOL YEARS. THERE ARE MANY FORMS OF EXCELLENCE IN EVERY CLASS. SOME OF YOU NOT CITED TODAY WILL GO ON TO IMPORTANT, OCCASIONALLY EVEN SPECTACULAR ACCOMPLISHMENTS--IN SOME CASES TO THE ASTONISHMENT OF YOUR CLASSMATES AND TEACHERS. AOA WILL EVENTUALLY RECOGNIZE SOME OF YOU BY ELECTION AS ALUMNI OR FACULTY MEMBERS. OTHERS WILL RECEIVE THE GRATITUDE AND ESTEEM OF YOUR PATIENTS--PERHAPS THE HIGHEST HONOR OF ALL.

MY GENUINE PLEASURE AT PARTICIPATING IN THIS SEMINAR IS FLAVORED WITH A BIT OF NOSTALGIA. PRIOR TO COMING TO MY PRESENT POSITION MORE THAN SEVEN MONTHS AGO, A LARGE SHARE OF MY PROFESSIONAL CAREER HAD BEEN DEVOTED TO MEDICAL EDUCATION. CONSEQUENTLY, AN OCCASION FOR MEETING WITH STUDENTS AND FACULTY BECOMES A KIND OF REUNION FOR ME. I ALSO RECALL THAT AN EXTRA-CURRICULAR LECTURE ISN'T ALWAYS CONSIDERED BY BUSY MEDICAL STUDENTS OR FACULTY MEMBERS TO BE A CAUSE FOR CELEBRATION, AND SO I APPROACH THIS OPPORTUNITY WITH A SPECIAL SENSE OF RESPONSIBILITY FOR THE USE OF YOUR TIME.

EXCELLENCE IS ESSENTIALLY A RELATIVE TERM--NOT AN ABSOLUTE. THE WORD IMPLIES COMPETITION. STRICTLY SPEAKING, IT IS NOT POSSIBLE TO DESCRIBE EXCELLENCE IN A VACUUM. IF WE SAY THAT SOMETHING OR SOMEONE IS EXCELLENT, THE STATEMENT HAS LITTLE MEANING UNLESS WE CAN SUPPLY THE CONTEXT--"COMPARED WITH WHAT?" AS APPLIED TO THE INDIVIDUAL, ONE MIGHT TERM THE STANDARDS OF COMPARISON AS EXTERNAL--COMPETITION WITH OTHERS, AND INTERNAL--COMPETITION WITH SELF.

WE OFTEN REFER TO UNIVERSITIES OR RESEARCH INSTITUTIONS AS "CENTERS OF EXCELLENCE." IN DOING SO, WE ARE DESCRIBING NOT JUST A COLLECTION OF DISTINGUISHED SCIENTISTS AND EDUCATORS. THE EXCELLENCE IN SUCH CENTERS IS THE RESULT OF CONSTANT INTERACTION IN A CHALLENGING MILIEU THAT DRAWS OUT FROM STUDENTS, SCIENTISTS, AND FACULTY ALIKE THE EXTRA EFFORT AND DEDICATION THAT WOULD NOT BE DEMANDED IN A LESS COMPETITIVE SETTING. THIS IS WHY SUCH GREAT CARE IS EXERCISED IN SELECTING STUDENTS FOR ADMISSION TO MEDICAL SCHOOL. THE QUALITY OF A MEDICAL SCHOOL IS, TO A SUBSTANTIAL EXTENT, DETERMINED BY THE QUALITY OF THE STUDENTS IT ACCEPTS. THE NATURE OF THE COMPETITION AMONG STUDENTS IN A PROFESSIONAL SCHOOL DIFFERS FROM THAT OF THE UNDERGRADUATE YEARS, AND I WILL ADDRESS

THAT DIFFERENCE MORE SPECIFICALLY IN A MOMENT. BUT INTERACTIONS AMONG MEDICAL STUDENTS ARE SUCH THAT AN OUTSTANDING FRESHMAN CLASS TENDS TO BE OUTSTANDING THROUGH GRADUATION--AND TO EXERT A STIMULATING INFLUENCE ON ALL ITS CONTEMPORARIES FOR ITS FOUR-YEAR LIFE.

I NEED NOT TELL YOU THAT ADMISSION TO MEDICAL SCHOOL IS COMPETITIVE--REQUIRING A HIGH DEGREE OF DEMONSTRATED EXCELLENCE. SUCH EXCELLENCE WAS JUDGED IN LARGE MEASURE BY YOUR SUCCESS IN COPING WITH BACCALAUREATE ACADEMIC REQUIREMENTS. MORE THAN MOST, MEDICAL STUDENTS CAN APPRECIATE THE APTNESS OF THE WORD "CURRICULUM" WHEN APPLIED TO UNDERGRADUATE SCHOOL. IT CONVEYS THE IMAGE OF A RACE THROUGH ITS LATIN ROOT, THE VERB MEANING "TO RUN."

DURING YOUR SPRINTS IN RUNNING THE COURSES REQUIRED FOR GRADUATION FROM COLLEGE, YOU HAVE BEEN CONSTANTLY REMINDED OF THE PACE REQUIRED OF THOSE WHO WOULD EXCEL.

BY NOW, HOWEVER, YOU HAVE BECOME MORE OF A LONELY LONG-DISTANCE RUNNER, AND YOU MUST SET YOUR OWN PACE. YOU ARE NO LONGER RUNNING AGAINST OUTSIDE COMPETITION. YOU ARE RUNNING AGAINST YOURSELF. RUNNING TO REACH YOUR OWN POTENTIAL!

WHAT WE SHOULD AIM AT PRODUCING IS MEN WHO POSSESS BOTH CULTURE AND EXPERT KNOWLEDGE IN SOME SPECIAL DIRECTION. THEIR EXPERT KNOWLEDGE WILL GIVE THEM THE GROUND TO START FROM, AND THEIR CULTURE WILL LEAD THEM AS DEEP AS PHILOSOPHY AND AS HIGH AS ART.

"WE HAVE TO REMEMBER THAT THE VALUABLE INTELLECTUAL DEVELOPMENT IS SELF-DEVELOPMENT."[1]

THIS IS NOT TO SAY THAT THE DISCIPLINE AND SUBSTANCE OF EDUCATION ARE UNIMPORTANT, FOR OBVIOUSLY THEY ARE IMPORTANT.

WHITEHEAD COMMENTED ONCE THAT SO FAR AS MERELY IMPARTING INFORMATION IS CONCERNED, NO UNIVERSITY HAS HAD ANY JUSTIFICATION FOR EXISTENCE SINCE THE PRINTING PRESS MADE BOOKS WIDELY AVAILABLE. THE JUSTIFICATION FOR A UNIVERSITY, HE SAID, "IS THAT IT PRESERVES THE CONNECTION BETWEEN KNOWLEDGE AND THE ZEST OF LIFE, BY UNITING THE YOUNG AND THE OLD IN THE IMAGINATIVE CONSIDERATION OF LEARNING . . . THIS ATMOSPHERE OF EXCITEMENT, ARISING FROM IMAGINATIVE CONSIDERATION, TRANSFORMS KNOWLEDGE. A FACT IS NO LONGER A BARE FACT: IT IS INVESTED WITH ALL ITS POSSIBILITIES. IT IS

AS YOU ADVANCE IN TRAINING AND EXPERIENCE, ANOTHER AND EVEN MORE DEMANDING SET OF STANDARDS COMES INTO PLAY FOR EACH OF YOU; FOR IT IS THEN THAT YOUR PERSONAL DEFINITION OF EXCELLENCE AND YOUR RESPONSES TO IT DETERMINE THE LEVEL OF YOUR COMPETENCE TO FULFILL THE HIGH PROMISE WITH WHICH YOUR CAREERS OF SERVICE WERE BEGUN. THE ANSWER TO THE QUESTION "COMPARED WITH WHAT?" ULTIMATELY MUST COME FROM WITHIN.

WHAT IS THE SOURCE OF THESE INTERNAL STANDARDS? I PERSONALLY BELIEVE THAT "EXCELLENCE GENES" ARE FAR MORE WIDELY DISTRIBUTED IN THE POPULATION THAN IS GENERALLY REALIZED. ONE OF THE FUNCTIONS OF EDUCATION IS TO MAKE IT POSSIBLE FOR INDIVIDUALS TO ACHIEVE IN WAYS THEY THOUGHT WERE BEYOND THEIR CAPABILITIES.

IN HIS ESSAYS ON "THE AIMS OF EDUCATION," ALFRED NORTH WHITEHEAD USED THE TERM "CULTURE" IN DISCUSSING THE DEVELOPMENT OF THE CONSCIOUSNESS OF QUALITY.

"CULTURE," HE SAID, "IS ACTIVITY OF THOUGHT, AND RECEPTIVENESS TO BEAUTY AND HUMANE FEELING. SCRAPS OF INFORMATION HAVE NOTHING TO DO WITH IT. A MERELY WELL-INFORMED MAN IS THE MOST USELESS BORE ON GOD'S EARTH.

NO LONGER A BURDEN ON THE MEMORY: IT IS ENERGIZING AS THE POET OF OUR DREAMS AND AS THE ARCHITECT OF OUR PURPOSES."[2]

BY THE TIME YOU ENTERED MEDICAL SCHOOL, IT IS SAFE TO SAY THAT YOUR PERSONAL STANDARDS OF EXCELLENCE WERE IN GREAT MEASURE DEVELOPED THROUGH THE HABITS ACQUIRED IN YOUR PREVIOUS SCHOOLING AND YOUR IMAGINATIVE CONSIDERATION OF KNOWLEDGE.

FIVE YEARS AGO, THE PRESIDENTS OF FIFTEEN LEADING AMERICAN UNIVERSITIES JOINTLY AUTHORED A REPORT CALLED "RESEARCH UNIVERSITIES AND THE NATIONAL INTEREST." IN THE REPORT, THE PRESIDENTS MADE A GENERAL STATEMENT WHICH, WITHOUT MENTIONING THE WORD, IS A USEFUL COMMENTARY ON EXCELLENCE.

"FIRST-RATE WORK IN ANY FIELD OF HUMAN ACTION IS RARE AND DIFFICULT," THEY SAID, "BUT NOWHERE IS THE QUALITY OF WORK MORE DECISIVE THAN IN HIGHER LEARNING AND RESEARCH. IT IS HARD TO TELL IN ADVANCE WHO WILL DO FIRST-CLASS SCHOLARLY AND SCIENTIFIC WORK. SOMETIMES SUCH WORK IS RECOGNIZED ONLY SLOWLY. MOREOVER, WHEN A PROBLEM IS EXTRAORDINARILY

RESISTANT, EVEN FIRST-CLASS WORK CAN FAIL. BUT NONE OF THESE QUALIFICATIONS DETRACTS FROM THE FORCE OF THE PROPOSITION THAT IT IS QUALITY THAT COUNTS. IN THE SIMPLE WORDS OF PHILIP HANDLER, PRESIDENT OF THE NATIONAL ACADEMY OF SCIENCES, 'IN SCIENCE, THE BEST IS VASTLY MORE IMPORTANT THAN THE NEXT BEST.'"[3]

IN THEIR COMMENT, THE FIFTEEN PRESIDENTS SUGGESTED A LONGITUDINAL DIMENSION OF EXCELLENCE--INVOLVING THE PASSAGE OF TIME. IT ADDS A USEFUL PERSPECTIVE TO OUR CONSIDERATIONS.

FOR EXCELLENCE IS ALSO AN EPHEMERAL TERM. WHAT IS EXCELLENT TODAY MAY TOMORROW BE MEDIOCRE. SO THE PERSON WHO WOULD BE EXCELLENT IN ANY FIELD MUST BE CURRENTLY INFORMED--THAT IS TO SAY--SUSTAINED EXCELLENCE IS UTTERLY DEPENDENT UPON CONTINUED LEARNING.

THERE IS NOTHING REVOLUTIONARY IN THAT STATEMENT. JOHN GARDNER REMARKED THAT "COMMENCEMENT SPEAKERS ARE FOND OF SAYING THAT EDUCATION IS A LIFELONG PROCESS. AND YET, HE ADDED, "THAT IS SOMETHING THAT NO YOUNG PERSON WITH A GRAIN OF SENSE NEEDS TO BE TOLD."

HE THEN ASKED, "WHY DO SPEAKERS GO ON SAYING IT?" AND SUPPLIED AN ANSWER. "IT ISN'T THAT THEY UNDERESTIMATE THEIR AUDIENCE. THE TRUTH IS THAT THEY KNOW SOMETHING THEIR YOUNG LISTENERS DO NOT KNOW--SOMETHING THAT CAN NEVER BE FULLY COMMUNICATED.

"NO MATTER HOW FIRM AN INTELLECTUAL GRASP THE YOUNG PERSON MAY HAVE ON THE IDEA THAT EDUCATION IS A LIFELONG PROCESS, HE CAN NEVER KNOW IT WITH THE POIGNANCY, WITH THE DEEPLY ETCHED CLARITY, WITH THE OVERTONES OF SATISFACTION AND REGRET THAT AN OLDER PERSON KNOWS IT. THE YOUNG PERSON HAS NOT YET MADE ENOUGH MISTAKES THAT CANNOT BE REPAIRED. HE HAS NOT YET PASSED ENOUGH FORKS IN THE ROAD THAT CANNOT BE RETRACED."

THEN GARDNER ADDED A KIND OF DISCLAIMER THAT NEATLY PUTS US IN OUR PLACE AND, AT THE SAME TIME, CONVEYS A WISE OBSERVATION ABOUT LEARNING. HE NOTED THAT "THE COMMENCEMENT SPEAKER MAY GIVE IN TO THE TEMPTATION TO MAKE IT SOUND AS THOUGH THE LEARNING EXPERIENCES OF THE OLDER GENERATION WERE ALL DELIBERATE AND A TRIUMPH OF CHARACTER--CHARACTER THAT THE YOUNGER GENERATION SOMEHOW LACKS." "IT IS NOT EASY," GARDNER SAYS, "TO TELL YOUNG PEOPLE HOW UNPURPOSEFULLY WE LEARN, HOW

LIFE TOSSES US HEAD OVER HEELS INTO OUR MOST VIVID LEARNING EXPERIENCES, HOW INTENSELY WE RESIST MANY OF THE INCREMENTS IN OUR OWN GROWTH."[4]

GARDNER SEEMS TO BE SAYING THAT WE MAY LEARN THE MOST WHEN WE ENCOUNTER PROBLEMS WE DON'T KNOW HOW TO HANDLE AND FROM WHICH WE CAN'T RETREAT. SUCH UNANTICIPATED CIRCUMSTANCES CAN SEVERELY TEST OUR PERSONAL CONCEPT OF EXCELLENCE AND CHALLENGE OUR COMMITMENT TO HIGH STANDARDS.

EXCELLENCE HAS MANY FACETS. JAMES B. CONANT REMARKED THAT "EACH HONEST CALLING, EACH WALK OF LIFE HAS ITS OWN ELITE, ITS OWN ARISTOCRACY BASED UPON EXCELLENCE OF PERFORMANCE."[5]

WITH A SOMEWHAT NARROWER FOCUS, JOHN GARDNER SUGGESTED THAT ". . .IF ONE LOOKS AT A GROUP OF MATURE SCIENTISTS--IN THEIR FIFTIES, LET US SAY--ONE FINDS THAT THOSE WHO ARE RESPECTED HAVE GAINED THEIR REPUTATIONS THROUGH EXERCISING A REMARKABLE VARIETY OF TALENTS. ONE IS HONORED FOR HIS EXTRAORDINARY GIFTS AS A TEACHER: HIS STUDENTS ARE HIS GREAT CONTRIBUTION TO THE WORLD. ANOTHER IS RESPECTED FOR THE PENETRATING IDEAS HE PUTS INTO THE STREAM OF SCIENCE.

ANOTHER IS RESPECTED--THOUGH PERHAPS NOT LOVED--FOR HIS DEVASTATING CRITICAL FACULTIES. AND SO THE LIST GOES. SOME ARE SPECIALISTS BY NATURE, SOME GENERALISTS; SOME CREATIVE, SOME PLODDING; SOME GIFTED IN ACTION, SOME IN EXPRESSION."[6]

SHEER TALENT DOES NOT EQUATE TO EXCELLENCE. KEEPING FULLY INFORMED IS ESSENTIAL TO BUT DOES NOT GUARANTEE MAINTENANCE OF EXCELLENCE. IT IS ULTIMATELY THE QUALITY OF PERFORMANCE THAT COUNTS.

A CENTURY AND A HALF AGO, THE GERMAN PHILOSOPHER HEGEL EXPOUNDED HIS BELIEF THAT THOUGHT AND LEARNING ALWAYS FOLLOWED A CYCLIC PATTERN BY WHICH WHAT IS IMPLICIT EVENTUALLY BECOMES EXPLICIT. THIS PASSAGE FROM THE IMPLICIT TO THE EXPLICIT, ACCORDING TO HEGEL, OCCURS IN THREE STAGES--THESIS, ANTITHESIS, AND SYNTHESIS. A HUNDRED YEARS LATER, WHITEHEAD USED THE HEGELIAN ANALYSIS TO DESCRIBE THE RHYTHM OF EDUCATION. WHITEHEAD'S DISCUSSION APPLIES APTLY TO THE PROCESS OF THE PHYSICIAN'S EDUCATION AND TO THE DEVELOPMENT OF EXCELLENCE.

RATHER THAN USING THE MORE CLASSICAL TERMINOLOGY--THESIS, ANTITHESIS, AND SYNTHESIS, WHITEHEAD TRANSLATED THE

NAMES OF THE THREE STEPS AS THE "STAGE OF ROMANCE," THE "STAGE OF PRECISION," AND THE "STAGE OF GENERALIZATION."

"THE STAGE OF ROMANCE," HE SAID, "IS THE STAGE WHEN A SUBJECT HAS THE VIVIDNESS OF NOVELTY HOLDING WITHIN ITSELF FASCINATING AND UNEXPLORED CONNECTIONS WITH POSSIBILITIES HALF-DISCLOSED BY GLIMPSES AND HALF-CONCEALED BY THE WEALTH OF MATERIAL."[7] YOU AS STUDENTS WERE IN THE STAGE OF ROMANCE WHEN YOU MADE THE DECISION THAT MEDICINE IS THE CAREER YOU MUST PURSUE. UNTIL YOU MAKE UP YOUR MIND ABOUT THE BRANCH OF MEDICINE YOU WILL PURSUE, YOU REMAIN IN THE STAGE OF ROMANCE.

WHITEHEAD CHARACTERIZED THE STAGE OF ROMANCE AS A FERMENT. AND THE SECOND STEP--THE STAGE OF PRECISION--AS THE TIME FOR SETTING IN ORDER A FERMENT ALREADY STIRRING IN THE MIND.

IN THE STAGE OF PRECISION, HE SAID, "WIDTH OF RELATIONSHIP IS SUBORDINATED TO EXACTNESS OF FORMULATION." HE CALLED IT THE "STAGE OF GRAMMAR--THE GRAMMAR OF LANGUAGE AND THE GRAMMAR OF SCIENCE."[7]

FOR THE PHYSICIAN-TO-BE, THE CHOICE OF RESIDENCY AND, FOR SOME OF YOU, OF A SPECIALTY REPRESENTS THE STAGE OF PRECISION. FOR THE RESEARCHER, THE STAGE OF PRECISION IS RIGOROUS FORMULATION OF THE PROBLEM TO BE STUDIED.

THE FINAL STAGE OF GENERALIZATION IN WHITEHEAD'S ILLUSTRATION IS A RETURN TO THE DRIVE AND FERMENT OF ROMANTICISM "WITH THE ADDED ADVANTAGE OF CLASSIFIED IDEAS AND RELEVANT TECHNIQUE. IT IS THE FRUITION WHICH HAS BEEN THE GOAL OF PRECISE TRAINING. IT IS THE FINAL SUCCESS."[7]

FRUITION INTO CREATIVITY AND EXCELLENCE COULD NOT HAPPEN WITHOUT THE INITIAL FERMENT WHICH IS ALMOST A RANDOM HAPPENING AND THE PERIOD OF DISCIPLINE WHICH IS ITS OPPOSITE. BUT BOTH THE FERMENT AND THE DISCIPLINE COME TO NOTHING UNLESS THEY ARE JOINED IN ACTION.

"TO BE WORTHY TO SERVE THE SUFFERING" IS NOT ENOUGH. THIS EXCELLENCE SOON FADES UNLESS IT IS PUT TO RISK IN SERVICE.

A MOMENT AGO, I USED THE TERM "CREATIVITY." IT IS A WORD THAT ALMOST INEVITABLY COMES TO MIND WHEN THINKING ABOUT EXCELLENCE. IT MIGHT ROUGHLY BE DEFINED AS DYNAMIC EXCELLENCE--A QUALITY CORRESPONDING TO WHITEHEAD'S "STAGE OF GENERALIZATION."

CREATIVITY TAKES MANY FORMS. IT IS NOT CONFINED TO THE LABORATORY, BUT WHEREVER IT IS APPLIED--IN THE PRACTICE OF MEDICINE--IN TEACHING--IN ADMINISTRATION, IT CARRIES WITH IT THE SPIRIT OF INQUIRY AND THE APPLICATION OF CURIOSITY AND IMAGINATION, LEADING TO NOVELTY AND DISCOVERY.

IMAGINATION IS A KIND OF LATENT CREATIVITY. IT IS NATURAL FOR YOUNG PEOPLE TO BE IMAGINATIVE, AND IF THIS IMAGINATION CAN BE COUPLED WITH DISCIPLINE, ITS ENERGY CAN BE A LIFELONG STRENGTH. WHITEHEAD REMARKED THAT A "TRAGEDY OF THE WORLD IS THAT THOSE WHO ARE IMAGINATIVE HAVE BUT SLIGHT EXPERIENCE, AND THOSE WHO ARE EXPERIENCED HAVE FEEBLE IMAGINATION"; AND THAT "FOOLS ACT ON IMAGINATION WITHOUT KNOWLEDGE; PEDANTS ACT ON KNOWLEDGE WITHOUT IMAGINATION."[8]

BOTH EXCELLENCE AND CREATIVITY ARE THE PRODUCT OF AN AMPLE STORE OF KNOWLEDGE HELD IN AN ACTIVE MIND.

IT IS NOT EASY TO DESCRIBE THE PROCESS OF CREATIVITY. SIR WILLIAM OSLER HAD HIS SIMPLE EXPLANATION FOR THE CREATIVITY THAT HAS LED TO PROGRESS IN MEDICINE. HE SAID, "(A) MASTER WORD . . . IS DIRECTLY RESPONSIBLE FOR ALL ADVANCES IN MEDICINE OVER THE PAST TWENTY-FIVE CENTURIES . . . THE MASTER WORD IS WORK."[9]

BUT IN SIR ALEXANDER FLEMING'S ACCOUNT OF THE DISCOVERY OF PENICILLIN, A DRASTICALLY DIFFERENT QUALITY OF CREATIVITY IS SUGGESTED; NAMELY, THE ADDED INGREDIENT OF CHANCE. HE SAID, "THERE ARE THOUSANDS OF DIFFERENT MOLDS AND THERE ARE THOUSANDS OF DIFFERENT BACTERIA, AND THAT CHANCE PUT THAT MOLD IN THE RIGHT SPOT AT THE RIGHT TIME WAS LIKE WINNING THE IRISH SWEEPSTAKES."[10]

THE GREAT FRENCH SCIENTIST, CLAUDE BERNARD, ECHOED FLEMING'S COMMENT ABOUT THE ACCIDENTAL NATURE OF CREATIVITY, BUT ADDED A MOST IMPORTANT DIMENSION TO THE THOUGHT. BERNARD SAID THAT "EXPERIMENTAL IDEAS ARE VERY OFTEN BORN BY CHANCE AS A RESULT OF FORTUITOUS OBSERVATIONS. NOTHING IS MORE COMMON, AND IT IS REALLY THE SIMPLEST WAY TO BEGIN A PIECE OF SCIENTIFIC WORK. WE WALK, SO TO SPEAK, IN THE REALM OF SCIENCE AND WE PURSUE WHAT HAPPENS TO PRESENT ITSELF ACCIDENTALLY TO OUR EYES."[11]

THE SAME THOUGHT WAS ECONOMICALLY EXPRESSED BY FRANKLIN P. ADAMS WHEN HE SAID, "I FIND THAT A GREAT PART OF THE INFORMATION I HAVE WAS ACQUIRED BY LOOKING UP SOMETHING AND FINDING SOMETHING ELSE ON THE WAY."[12]

PERHAPS IT IS USEFUL TO EMPHASIZE THE FACT THAT THE ADAMS PROCESS WAS BEGUN BY LOOKING UP SOMETHING. SERENDIPITY IS A DIVIDEND OF ACTIVITY.

LINCOLN STEFFANS, CALLED BY SOME AN AMERICAN SOCRATES BECAUSE HIS ARTICLES AND LECTURES WERE FILLED WITH UNANSWERED QUESTIONS, ASKED, "HOW DOES ONE TRAIN A STUDENT IN THE TECHNIQUES OF DISCOVERY?" IN THIS INSTANCE, HE GAVE A RESPONSE BY ANSWERING "I HAVE NEVER SEEN ANYBODY IMPROVE ON THE ART AND TECHNIQUE OF INQUIRY BY ANY OTHER MEANS THAN ENGAGING IN INQUIRY."

THE BRITISH NOBEL LAUREATE, PETER MEDAWAR, SUMMARIZED THE PARADOX OF SCIENTIFIC CREATIVITY BY SAYING THAT "A SCIENTIST MUST INDEED BE FREELY IMAGINATIVE AND YET SKEPTICAL, CREATIVE AND A CRITIC. THERE IS A SENSE IN WHICH HE MUST BE FREE, BUT ANOTHER IN WHICH HIS THOUGHT MUST BE VERY PRECISELY REGIMENTED; THERE IS POETRY IN SCIENCE, BUT ALSO A LOT OF BOOK KEEPING."[13]

LAST WEEK, WHILE PARTICIPATING IN THE CENTENNIAL OBSERVANCES OF THE UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER, I TALKED WITH DR. JAMES H. AUSTIN, PROFESSOR AND HEAD OF THE DEPARTMENT OF NEUROLOGY THERE. DR. AUSTIN HAS WRITTEN EXTENSIVELY ON CREATIVITY--AND RECENTLY HAS DEVOTED A BOOK TO THE SUBJECT TITLED, "CHASE, CHANCE AND CREATIVITY--THE LUCKY ART OF NOVELTY."

IN AUSTIN'S EXAMINATION OF SERENDIPITY, HE IDENTIFIES FOUR DISTINCT FORMS OF CHANCE: ACCIDENTAL GOOD LUCK: ENERGETIC MOTOR ACTIVITIES IN THE RIGHT TERRITORY; A SPECIAL KIND OF RECEPTIVITY AND DISCERNMENT UNIQUE TO THE RECIPIENT: AND A PROBING ACTION WITH A DISTINCTIVE PERSONAL FLAVOR WHICH COURTS DAME FORTUNE."

HIS BOOK IS FILLED WITH ACCOUNTS OF HIS PERSONAL EXPERIENCES AS A CLINICIAN AND SCIENTIST, AND HE DRAWS FROM THESE EXPERIENCES A DEMONSTRATION OF THE ROLE OF CREATIVITY IN TEACHING, RESEARCH, AND PRACTICE.

ANY DISCUSSION OF CHANCE AND CREATIVITY IN SCIENCE IS INCOMPLETE WITHOUT THE MODERATING WORDS OF LOUIS PASTEUR--"CHANCE FAVORS ONLY THE PREPARED MIND."

THROUGHOUT ALL OF THESE CHARACTERIZATIONS OF CREATIVITY, THERE ARE THE CONTRADICTORY CONCEPTS THAT WOULD SPELL DISASTER FOR A MARKSMAN. THEY SEEM TO BE SAYING THAT YOU SHOULD AIM CAREFULLY--BUT NOT EXPECT TO HIT THE TARGET IN YOUR SIGHTS. IT BRINGS TO MIND THE ADVICE GIVEN TO NIGHT FLYERS DURING WORLD WAR II WHO WERE TOLD THAT DIMLY LIT OBJECTS COULD ONLY BE SEEN IF YOU DID NOT LOOK DIRECTLY AT THEM.

CREATIVE EXCELLENCE IS USUALLY APPROACHED INDIRECTLY. THERE ARE OFTEN LONG PERIODS WHEN THE PERSON WHO IS ABOUT TO MAKE AN ORIGINAL OBSERVATION APPEARS TO DO NOTHING BUT TAKE IN INFORMATION, WORK RATHER FRUITLESSLY AT SEEMINGLY TRIVIAL ASPECTS OF THE PROBLEM, OR GIVE ATTENTION TO UNRELATED MATTERS. THIS IS SOMETIMES DESCRIBED AS A PERIOD OF "INCUBATION."

FOLLOWING SUCH A PHASE, THE SOLUTION OF A DIFFICULT PROBLEM, OR THE OCCURRENCE OF AN ORIGINAL IDEA, WILL OFTEN COME ALL OF A SUDDEN IN A LEAP OF INSIGHT. IT USUALLY RESULTS FROM A DRAMATIC CHANGE IN THE WAY THE PROBLEM IS PERCEIVED. SUCH A TRANSFORMATION CAN CHANGE A COMPLICATED PROBLEM INTO A SIMPLE ONE AND THIS SEQUENCE CAN BE AS DESCRIPTIVE OF A DIFFICULT DIAGNOSIS AS OF A STUBBORN RESEARCH PROBLEM.

TWO GREAT ENEMIES OF CREATIVITY ARE MENTAL RIGIDITY ON THE ONE HAND AND WISHFUL THINKING ON THE OTHER. THESE ARE EVIDENT WHEN A PERSON ACTS EITHER IN A FAR MORE REGULAR WAY THAN THE SITUATION DEMANDS OR ELSE IS INCAPABLE OF PERCEIVING THE EXTERNAL REALITIES THAT MAKE HIS IDEAS INFEASIBLE.

THESE BARRIERS TO CREATIVITY ARE OF THE MOST DIFFICULT KIND BECAUSE THEY ARE SELF-IMPOSED. WE TEND TO GIVE UNDUE IMPORTANCE TO ESTABLISHED PATTERNS OF THOUGHT AND LOCK OURSELVES INTO CONFORMITY WITH THEM. WE FEAR TO CHALLENGE THE OBVIOUS LEST WE APPEAR NAIVE. FOR SOME, THIS FEAR MAY BE AN INSURMOUNTABLE BARRIER. JACQUES BARZUN ONCE REMARKED THAT ONE CANNOT LEARN TO ICE SKATE OR SPEAK FRENCH WITHOUT LOOKING FOOLISH[14]--AND THAT'S WHY THESE SKILLS ARE EASY TO THE YOUNG WHO DO NOT WORRY SO MUCH ABOUT APPEARANCES.

BRAINSTORMING IS AN EFFICIENT TECHNIQUE FOR TAPPING THE CREATIVE IDEAS OF A GROUP. IT WORKS BEST WHEN THE MEMBERS OF THE GROUP CAN SUSPEND JUDGMENT--SAVING CRITICAL EVALUATION OF IDEAS FOR LATER; WHEN IDEAS ARE PRESENTED WITHOUT INHIBITION WHETHER THEY ARE GOOD OR BAD, SENSIBLE OR SILLY; WHEN THERE IS A SUBSTANTIAL NUMBER OF IDEAS

PRESENTED, AND WHEN THERE IS CROSS-FERTILIZATION-EXAMINATION OF EACH OF THE IDEAS FROM THE DIFFERENT PERSPECTIVES OF THE INDIVIDUALS IN THE GROUP.

WHILE THESE GUIDELINES PERTAIN TO GROUP CONSIDERATION, THEY HAVE VALID COUNTERPARTS IN THE PROCESS BY WHICH AN INDIVIDUAL GENERATES CREATIVE QUESTIONS AND ANSWERS.

YOU WILL BE CALLED UPON TIME AND AGAIN, IN WHATEVER CAREER OPTIONS YOU MAY CHOOSE, TO EXERCISE CREATIVITY. HISTORICALLY, EACH PHYSICIAN HAS HAD A TRIPLE OBLIGATION--TO SERVE--TO TEACH--AND TO SEARCH. ALTHOUGH THE EMPHASIS PLACED ON ONE OR MORE OF THESE OBLIGATIONS DIFFERS FROM PERSON TO PERSON IN THE CAREERS THEY CHOOSE FOR THEMSELVES, THE TRIAD IS ALWAYS PRESENT.

OUR SERVICE OF THE SUFFERING CAN TAKE A VARIETY OF FORMS. IN RECENT YEARS WE HAVE SEEN THE POWERFUL BENEFITS OF INCREASED KNOWLEDGE.

IN AN ESSAY "ON THE SCIENCE AND TECHNOLOGY OF MEDICINE," LEWIS THOMAS ADDRESSED THE QUESTION OF MEDICAL CARE IN GLOBAL TERMS. "IF," HE SAID, "OUR SOCIETY WISHES

TO BE RID OF THE DISEASES, FATAL AND NON-FATAL, THAT PLAGUE US THE MOST, THERE IS REALLY LITTLE PROSPECT OF DOING SO BY MOUNTING A STILL LARGER HEALTH-CARE SYSTEM AT STILL GREATER COST FOR DELIVERING ESSENTIALLY TODAY'S KIND OF TECHNOLOGY ON A LARGER SCALE. WE WILL NOT DO SO BY CARRYING OUT BROADER PROGRAMS OF SURVEILLANCE AND SCREENING. THE TRUTH IS THAT WE DO NOT YET KNOW ENOUGH."

BUT THERE IS ALSO ANOTHER TRUTH OF GREAT IMPORTANCE: WE ARE LEARNING FAST. THE HARVEST OF NEW INFORMATION FROM THE BIOLOGICAL REVOLUTION OF THE PAST QUARTER-CENTURY IS JUST NOW COMING IN, AND WE CAN PROBABLY BEGIN NOW TO FIGURE OUT THE MECHANISMS OF MAJOR DISEASES WHICH WERE BLANK MYSTERIES A FEW YEARS BACK AS ACCURATELY AND PROFITABLY AS WAS DONE FOR THE INFECTIOUS DISEASES EARLIER IN THIS CENTURY. THIS CAN BE SAID WITH CONSIDERABLE CONFIDENCE, AND WITHOUT RISK OF OVERPROMISING OR RAISING FALSE HOPES, PROVIDED WE DO NOT SET TIME SCHEDULES OR OFFER DATES OF DELIVERY. SOONER OR LATER IT WILL GO THIS WAY, SINCE CLEARLY IT CAN GO THIS WAY. IT IS SIMPLY A QUESTION AT THIS STAGE OF EVENTS OF HOW MUCH WE WISH TO INVEST, FOR THE HEALTH-CARE SYSTEM OF THE FUTURE, IN SCIENCE."[15]

SUCH PUBLIC INVESTMENT IN SCIENCE COMES DOWN TO A HIGHLY PERSONAL AND INDIVIDUAL ACTIVITY. AS ALAN GREGG HAS SAID, "MEDICAL RESEARCH IS AN ABSTRACTION--THE REALITIES ARE NOT THE LABORATORIES AND THE HOSPITALS BUT THE MEN (AND WOMEN) WHO SEARCH AGAIN AND AGAIN FOR CAUSES."[16]

IT IS FOR THIS REASON THAT THE NATIONAL INSTITUTES OF HEALTH HAS RECOGNIZED PRACTICALLY SINCE THE BEGINNING OF ITS EMERGENCE AS THE PRINCIPAL BIOMEDICAL RESEARCH ARM OF THE FEDERAL GOVERNMENT THAT THE SUPPORT OF RESEARCH AND TRAINING MUST GO HAND IN HAND. OUR COMMITMENT TO RESEARCH TRAINING HAS REMAINED FIRM.

SINCE BECOMING DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH, I HAVE BECOME EVEN MORE STRONGLY CONVINCED THAN BEFORE OF THE VITAL IMPORTANCE OF ATTRACTING THE BEST AND BRIGHTEST TO CAREERS IN RESEARCH--ESPECIALLY THE NEED TO INTEREST AND HOLD YOUNG MEN AND WOMEN WHO ARE TRAINED AS PHYSICIANS. IN MY STATEMENTS TO TOP OFFICIALS IN THE ADMINISTRATION, TO THE CONGRESS AND TO THE PUBLIC, THE NEED HAS BEEN A RECURRENT THEME--AND I PLAN TO CONTINUE THIS EMPHASIS.

JUST OVER A MONTH AGO, WE RECEIVED THE REPORT OF THE HOUSE COMMITTEE ON APPROPRIATIONS REGARDING THE PROPOSED 1983 BUDGET FOR THE NATIONAL INSTITUTES OF HEALTH--PERMIT ME TO READ A PARAGRAPH:

"THE COMMITTEE SHARES THE CONCERNS THAT HAVE BEEN EXPRESSED BY OFFICIAL AND PUBLIC WITNESSES ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS, ESPECIALLY AS ALL CLINICAL RESEARCH INVOLVING HUMAN PATIENTS MUST BE DONE BY--OR AT LEAST UNDER THE GUIDANCE OF--A QUALIFIED PHYSICIAN. IT IS APPARENT AND UNDERSTANDABLE THAT YOUNG PHYSICIANS CONSIDERING HEALTH CAREERS ARE OFTEN DISSUADED FROM APPLYING FOR RESEARCH TRAINING OR RESEARCH FELLOWSHIPS BY THEIR PERCEPTION OF INSTABILITY IN THE FEDERAL COMMITMENT TO RESEARCH AND BY THEIR AWARENESS THAT A RESEARCH CAREER REPRESENTS A SUBSTANTIAL SACRIFICE WHEN COMPARED WITH ALMOST ANY FORM OF MEDICAL PRACTICE. THE COMMITTEE WOULD LIKE NIH TO REVIEW THIS PROBLEM CAREFULLY AND TO SUGGEST WHAT STEPS MIGHT USEFULLY BE TAKEN TO INCREASE THE NUMBER OF YOUNG PHYSICIANS WHO WILL APPLY FOR RESEARCH TRAINING AND TO RETAIN THOSE WHO DO EMBARK ON RESEARCH CAREERS. THE COMMITTEE WILL EXPECT A REPORT ON THIS SUBJECT AT NEXT YEAR'S HEARINGS."[17]

EVEN WITHOUT THAT PRODDING, WE HAVE DEVOTED CONSIDERABLE ATTENTION TO THIS PROBLEM AND HAVE UNDER CONSIDERATION SOME MAJOR STEPS TOWARD ITS SOLUTION. YOU MAY BE SURE THAT THE PREPARATION OF THIS REPORT WILL RECEIVE OUR MOST CAREFUL ATTENTION.

IF THE OPPORTUNITY TO ENGAGE IN SUPPORTED RESEARCH IS HIGHLY UNCERTAIN, THE YOUNG PHYSICIAN COULD REASONABLY QUESTION THE WISDOM OF UNDERTAKING RESEARCH TRAINING. THIS IS A MAJOR REASON FOR OUR CONTINUED EMPHASIS OF THE NEED TO "STABILIZE" OUR OFFERING OF GRANTS FOR INVESTIGATOR-INITIATED PROJECT RESEARCH--TO PROVIDE A REASONABLE DEGREE OF ASSURANCE ABOUT FUTURE OPPORTUNITIES.

MORE THAN A HUNDRED YEARS AGO, OLIVER WENDELL HOLMES COMMENTED TO A GRADUATING CLASS THAT "SCIENCE IS A GREAT TRAVELER AND WEARS OUT SHOES PRETTY FAST, AS MIGHT BE EXPECTED."

SINCE THAT DAY, THE PACE OF SCIENCE, AND CONSEQUENTLY OF THE PRACTICE OF MEDICINE, HAS ACCELERATED TO A FANTASTIC RATE. PERHAPS IT IS SIGNIFICANT TO NOTE THAT MANY STATUES OF THE ROMAN GOD MERCURY HAD HIM NOT ONLY CARRYING A CADUCEUS BUT ALSO WEARING WINGED SANDALS.

IT MAY MIX MYTHOLOGY A BIT, BUT IT SEEMS TO ME THAT A MODERN PHYSICIAN MIGHT FAIRLY BE REPRESENTED BY THE FIGURE OF MERCURY CARRYING THE AESCULAPIAN STAFF OF HEALING AND WEARING THE WINGED SANDALS OF MODERN SCIENCE.

THE PRACTICE OF MEDICINE IS BOTH A SCIENCE AND AN ART. A SKILLED PHYSICIAN MUST HAVE EXTENSIVE MEDICAL KNOWLEDGE, WHICH IS THE BEDROCK OF TECHNICAL COMPETENCE. IN ADDITION, HE OR SHE MUST HAVE JUDGMENT, TACT, DECISIVENESS, RESTRAINT, COMPASSION, INTEREST, TIME, AND OTHER PERSONAL QUALITIES OF CARING AND DEDICATION. THE SCIENCE AND THE ART OF MEDICINE MUST ALWAYS BE INTIMATELY LINKED. THE STUDENT STUDIES THE SCIENCE OF MEDICINE FIRST, MASTERS IT EARLY, AND RETURNS TO IT FREQUENTLY. THE STUDENT ACQUIRES THE ART OF MEDICINE--THE SKILLFUL APPLICATION OF MEDICAL KNOWLEDGE IN THE OPTIMAL CARE OF THE PATIENT--MORE GRADUALLY AND WITH EXPERIENCE.

SINCE MEDICINE IS DERIVED FROM A NUMBER OF SCIENCES RELEVANT TO THE HEALTH OF INDIVIDUALS OR OF GROUPS, PHYSICIANS MUST BE SCIENTISTS TO UTILIZE THESE COMPLEX DISCIPLINES EFFECTIVELY.

TO BE A SCIENTIST, THE PHYSICIAN MUST HAVE MORE THAN ROTE SCIENTIFIC KNOWLEDGE, OR EVEN FLUENCY IN ITS PARTICULAR JARGON. PHYSICIANS MUST BE CONVERSANT WITH THE PROCESSES OF SCIENTIFIC INQUIRY--HOW DATA ARE OBTAINED AND EVALUATED; HOW HYPOTHESES ARE FRAMED, MODIFIED, OR DISCARDED; THE USES AND LIMITATIONS OF INDUCTIVE REASONING. IN SHORT THEY MUST UNDERSTAND SCIENCE AS AN INTELLECTUAL INSTRUMENT WHICH HAS BEEN SLOWLY PERFECTED OVER CENTURIES. ONLY IN THIS WAY CAN THEY REMAIN ATTENTIVE TO MEDICAL PROGRESS AS A CRITICAL AND INDEPENDENT PARTICIPANT. OTHERWISE THEY WILL BE IN DANGER OF BEING THE PASSIVE PURVEYOR OF MEDICAL FASHIONS. BOTH THE SPIRIT AND RIGOR OF SCIENCE ARE NECESSARY FOR THE PHYSICIAN TO BECOME AND REMAIN A SCHOLAR IN MEDICINE. MEDICAL PRACTICE ITSELF CONTAINS MANY OF THE ELEMENTS OF SCIENTIFIC INQUIRY IN THE PURSUIT AND EVALUATION OF DATA (HISTORY, PHYSICAL EXAMINATION, LABORATORY STUDIES) AND IN FRAMING A HYPOTHESIS (TENTATIVE CLINICAL DIAGNOSIS).

AS A SCIENTIST, THE PHYSICIAN IS THE BENEFICIARY OF BOTH THE FRUITS OF SCIENTIFIC RESEARCH AND OF THE MENTAL DISCIPLINE OF THE SCIENTIFIC METHOD. TO A GREATER OR LESSER DEGREE, THE PHYSICIAN ALSO HAS THE OPPORTUNITY TO CONTRIBUTE PERSONALLY TO MEDICAL PROGRESS. MOST MEDICAL

RESEARCH IS NOW CARRIED OUT BY TEAMS OF PARTICIPATING INVESTIGATORS IN ELABORATELY EQUIPPED LABORATORIES WHICH UTILIZE THE ADVANCED INSTRUMENTATION AND TECHNOLOGY OF MODERN SCIENCE. THERE IS STILL SCOPE, HOWEVER, FOR SCIENTIFIC CONTRIBUTIONS MADE BY INQUIRING PHYSICIANS BASED ON THEIR OWN EXPERIENCES IN PATIENT CARE. MUCH OF MEDICAL PROGRESS HAS DERIVED FROM THIS KIND OF CURIOSITY IN THE PAST. IN ADDITION, THIS FORM OF CLINICAL RESEARCH, ON WHATEVER MODEST SCALE IT MAY BE ENGAGED IN, ADDS EXCITEMENT AND ZEST TO PROFESSIONAL LIFE.

MY PREDECESSOR AS DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH AND LONGTIME FRIEND, DONALD S. FREDRICKSON, EXPRESSED SOME OF HIS VIEWS ON THE PRACTICING PHYSICIAN'S ROLE IN BIOMEDICAL RESEARCH IN AN ARTICLE THAT APPEARED IN JAMA LAST JUNE. HE SAID, "I ANTICIPATE A TIME WHEN A NATIONAL MEDICAL COMPUTER NETWORK WILL LINK ALL PHYSICIANS. THIS COULD REPRESENT A HUGE ADVANTAGE IN OUR ABILITY TO CONDUCT CERTAIN KINDS OF CLINICAL RESEARCH. FOR SEVERAL YEARS, ALL PHYSICIANS IN STOCKHOLM COUNTY IN SWEDEN HAVE BEEN SO CONNECTED. THERE THE PERSUADER IS A PRACTICAL ONE. IF THEY WANT TO BE REIMBURSED FOR THEIR SERVICES, THEY MUST PROVIDE CERTAIN BASIC INFORMATION, WHICH HAS COMMUNITY VALUE IN TERMS OF

EPIDEMIOLOGY, THE UTILIZATION OF SERVICES, AND THE ASCERTAINMENT OF OTHER HEALTH CARE TRENDS. SOME PHYSICIANS MAY FIND SUCH A SYSTEM TROUBLESOME, PARTICULARLY SINCE SOME FORM OF QUALITY CONTROL WILL INEVITABLY BE POSSIBLE THROUGH AN INFORMATION NETWORK. SOMETHING OF THIS SORT IS INEVITABLE, AND ONE OF THE DIVIDENDS WILL BE ASSISTANCE IN KEEPING ABREAST OF THE RISING TIDE OF NEW INFORMATION. WE ARE ALL GOING TO HAVE TO GET ON-LINE JUST TO KEEP UP.

"OUR MEDICAL SCHOOLS WILL HAVE TO TURN OUT STUDENTS WHO ARE ADEPT AT USING A COMPUTER KEYBOARD, WHO ARE BETTER TRAINED IN THE ASSESSMENT OF THE ACCURACY AND VALIDITY OF MEDICAL DATA, AND WHO HAVE GAINED AN UNDERSTANDING THAT MERELY COLLECTING INFORMATION IS NOT SCIENTIFIC RESEARCH. WE MAY ALSO HAVE TO PROVIDE AUGMENTED TRAINING IN STATISTICS AND IN THE HANDLING OF HYPOTHESES AND EVIDENCE. IF PHYSICIANS ARE PROPERLY PREPARED, THE PRESENT INFORMATION 'REVOLUTION' WILL COMPLEMENT THE BIOLOGIC ONE IN ALLOWING MORE PHYSICIANS TO PARTICIPATE IN THE PROCESS OF RESEARCH."[18]

WE HAVE SEEN WITHIN THIS GENERATION AN ALMOST UNBELIEVABLE EXPANSION OF KNOWLEDGE WHICH JUSTIFIES GREAT

OPTIMISM FOR THE EVENTUAL CONTROL AND CURE OF MAJOR DISEASES AND THE POSSIBLE ELIMINATION OF PREMATURE DEATH FROM ILLNESS. MEDICAL EDUCATORS ARE ALMOST OVERWHELMED BY WHAT AMOUNTS TO AN EMBARRASSMENT OF RICHES IN THE STOCK OF INFORMATION TO BE COMMUNICATED DURING TRAINING.

THE MEANING OF EXCELLENCE TODAY IMPLIES A MUCH HIGHER STANDARD OF COMPARISON THAN IT DID PREVIOUSLY AND IN CONSEQUENCE ENHANCES THE HONOR YOU HAVE BEEN ACCORDED BY ELECTION TO AOA IN SUCH A TIME. IT ALSO MEANS THAT MAINTENANCE OF EXCELLENCE WILL BE THAT MUCH TOUGHER IN THE EIGHTIES, THE NINETIES, AND AFTER THE TURN OF THE CENTURY.

ONE SUPREME ESSENTIAL OF HUMAN EXCELLENCE, HOWEVER, REMAINS UNCHANGED. WITHOUT IT, A PHYSICIAN ESPECIALLY IS SERIOUSLY FLAWED.

TO EXPRESS THIS THOUGHT, I WILL BORROW A PARAGRAPH FROM K. G. SAIYAIDAIN, INDIA'S SECRETARY OF EDUCATION, WHEN IN 1959 HE ADDRESSED AN ASSEMBLY AT TEACHERS COLLEGE OF COLUMBIA UNIVERSITY. IN WORDS OF CONSEQUENCE FOR THE SCHOOL YEARS AND YEARS BEYOND, HE REMINDED "IT IS A LONG AND ARDUOUS JOURNEY FROM <u>INFORMATION</u>, WHICH IS THE LOWLY

FOUNDATION OF KNOWLEDGE, TO VISION, WHICH IS ITS HIGHEST FRUIT. THROUGH THE IMPACT OF PERSONAL EXPERIENCE, INFORMATION ASSUMES THE ROLE OF KNOWLEDGE, BUT EVEN WHEN KNOWLEDGE COMES, WISDOM OFTEN LINGERS FAR BEHIND. WISDOM HAS BEEN DEFINED AS THE "GRACE OF KNOWLEDGE." IT IS ONLY WHEN KNOWLEDGE HAS BEEN PASSED INTO JUDGMENT AND BECOMES ASSIMILATED INTO GOOD BEHAVIOR THAT WISDOM IS BORN. AND WHEN WISDOM IS WELCOMED INTO THE SANCTUARY OF THE HEART AND BECOMES WEDDED TO EMOTIONS, IT PUTS ON THE MANTLE OF CHARITY AND COMPASSION."[19]

AN EXCELLENT PHYSICIAN MUST BE CLOTHED IN SUCH A MANTLE.

NOTES

[1]Alfred North Whitehead, The Aims of Education, New American Library of World Literature, Inc., New York, 1955, p. 13.

[2]Ibid., p. 97.

[3]"Research Universities and the National Interest," Ford Foundation, New York, 1978, p. 5.

[4]John W. Gardner, Excellence, Harper & Row, New York, 1962, pp. 138-139.

[5]Ibid., p. 132

[6]Ibid., p. 129

[7]Whitehead, pp. 29, 30, 31.

[8]Ibid., p. 98

[9]James H. Austin, Chase, Chance and Creativity, Columbia University Press, New York, 1978, p. 185.

[10]Ibid., p. 89

[11]Ibid., p. 1

[12]Ibid., p. 8

[13]Austin, p. 167

[14]Jacques Barzun, Teacher in America, Doubleday & Co., New York, 1959, p. 124.

[15]Lewis Thomas, M.D., "On the Science and Technology of Medicine," Doing Better and Feeling Worse, W. W. Norton & Co., New York, 1977.

[16]Austin, p. 191.

[17]United States, 97th Cong. 2nd Sess., 1982. H.Rpt. 97-894: Depts. of Labor, Health & Human Services, and Education, and Related Agencies Appropriations Bill, 1983, p. 28.

[18]Donald S. Fredrickson, M.D., "'Venice' is Not Sinking (The Water is Rising)," Journal of the American Medical Association, Vol. 247, No. 22, p. 3073, June 1982.

[19]K. G. Saiyaidain, Teachers College Address, Columbia University Press, 1959.

THE ROLE OF THE FEDERAL GOVERNMENT IN BIOMEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

As we begin, I want to thank you, Dr. Glenn, for inviting me to present the first E. Garland Herndon, Jr., guest lecture. The establishment of this lectureship is a statement of great esteem and warmth felt for an extraordinary man. I am sorry that Dr. Herndon cannot be present today at the inaugural lecture given in his honor, but I am aware of the substantial contributions he has made to this institution, first as Professor of Medicine and Director of the Clinical Research Center, and more recently as Vice President for Health Affairs and as Director of the Woodruff Medical Center, which embraces the health science units of Emory University. But I am not surprised to learn of his accomplishments. After all, he is a North Carolinian, born in North Carolina, educated in North Carolina, trained in North Carolina. I am pleased to join you in honoring this outstanding clinician, educator, administrator, and leader.

I am also pleased to be back in a medical school. It is a familiar and congenial atmosphere to me, as I was privileged to serve for 25 years at the Duke University Medical School, where I

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**Director, National Institutes of Health, Bethesda, Maryland 20205

was a colleague of your Dean, Jim Glenn, and of your Chairman of Pediatrics, George Brumley, two other distinguished North Carolinians.

I have been asked to speak on "The Role of the Federal Government in Biomedical Research." I am aware that I was invited to discuss this topic as the relatively new Director of the National Institutes of Health. I have now been in my position about eight months. It has been a time of extraordinary learning for me. One of the first things I learned was that I had to be careful in suggesting that something be done, because there was a high probability that someone would do it. I never had that problem at Duke. Another early surprise was the intensity of the interactions between NIH and a multitude of special interest groups and their Washington representatives, as well as with the Members of Congress. I was astonished to learn that sometimes Congressmen make deals in order to gain support for their pet projects, and also that the Administration sometimes abruptly changes its mind under interesting circumstances. I wasn't aware of that before. I now understand what is meant by the saying that there are two things you do not want to know how they are made. One is sausage and the other is legislation.

But irrespective of the process, many of the laws passed by Congress turn out to be wise, even visionary, and of enormous benefit to the American people. I include in that category the succession of laws that established and molded NIH. The origins of NIH go back to the Laboratory of Hygiene, established in 1887 as a component of the Public Health Service on Staten Island.

Thus, we are approaching our one hundredth anniversary. The Laboratory was later moved to Washington and, in 1930, was named the National Institute of Health. In 1937, the National Cancer Institute was established as a separate and coordinate entity. But prior to World War II the role of the American government in medical education and in biomedical research was minimal. Private foundations, voluntary organizations, and the professional societies were the dominant sources of support and influence in shaping medical education, funding research, and carrying out health promotion programs. When, out of wartime experience, it was recognized that Federal support of research was not only appropriate but essential, agencies like NIH were provided comparatively massive support. The Public Health Service Act of 1944 established the legislative basis for future developments. The National Institute of Health and the National Cancer Institute were merged. An order of the Surgeon General in 1947 established the Experimental Biology and Medicine Institute. In 1948, Congress created the National Heart Institute, the National Institute of Dental Research, and the National Microbiological Institute. The new agency was named the National Institutes of Health. In succeeding years several other Institutes, Bureaus, and Divisions were added so that we now have sixteen operating units and, incidentally, sixteen separate budgets to be negotiated with the Administration and the Congress each year.

My personal association with NIH goes back to 1951, when I joined the National Heart Institute in a position that, as far as

I knew, had no name. Now I would be called a clinical associate or a clinical staff fellow. At that time Dr. James A. Shannon was Associate Director in Charge of Research in the Heart Institute. When he became Director of NIH in 1955, its total budget was $82 million. When he retired as Director, thirteen years later, the NIH budget had passed $1 billion.

During Dr. Shannon's tenure, the basic mechanisms of support of biomedical science were established, and these have continued to serve us well. Jim Shannon insisted that congressional mandates to conduct research in cancer, heart disease, and arthritis, for example, be interpreted broadly. He realized that the science base did not exist to permit a frontal assault on the diseases themselves. He set about building the research capability of this country, both through the intramural program at NIH in Bethesda and through substantial expansion of the mechanism of grants-in-aid to institutions. Corollary objectives included strengthening the institutions in which biomedical research would be done, and development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and brightest young minds resident in the universities. Together with Hill-Burton money for clinical facilities, NIH construction funds for research facilities modified the topography of the academic medical center,indirectly changing--and most of us would say greatly strengthening--medical education.

NIH has proceeded on a course that, in many ways, was charted by a report written in 1945 by Vannevar Bush, the

President's Science Advisor, and greatly influencing congressional action in the immediately succeeding years. This report, Science--The Endless Frontier, outlined policies for Federal support of health research that have served the national interests so well since that time. The flavor and substance of the document stand up in sturdy perspective when viewed with the critical hindsight of nearly forty years. I would like to read a few sentences from it:

> "The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge . . . ."[1]

* * * * *

> "While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any extension of medical facilities must be accompanied by an expansion of medical training and research.
>
> "Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."[2]

Permit me to leap beyond Bush, and quote our current President's Science Advisor, Dr. George Keyworth. In a recent speech he stated, "Basic research warrants government support because it is an investment in the future--in a better quality of life, better security, a better economy, and simply better understanding."[3] In the same speech he emphasized that basic research was a responsibility of government for the dual reasons that it benefited the people and the economy, and that there was no other source of support for basic research on the scale required.

Support of biomedical science during the past three decades, chiefly by NIH, has transformed our knowledge and understanding of biology. The transformation has been so dramatic, so pervasive, that it justifies the use of the overworked term "revolution." Never in the history of biological science has there been so much exciting work going on, so many exquisitely promising leads in so many fields, or such an army of brilliant scientists at work in their laboratories or at their blackboards. Molecular biology, which began in the 1950s as an exhilarating intellectual adventure in bacterial genetics, with no predictable public benefit, through recombinant DNA technology has permeated all branches of biological science. Human insulin is being produced by bacteria. In India, agricultural scientists are exploring how nitrogen fixation genes can be insinuated into wheat and rice. The discovery of oncogenes has provided a new paradigm for cancer research. In immunology the once obscure flocculations and precipitations of test-tube scientists have given us a wholly new insight into a range of human diseases and,

in the instance of monoclonal antibodies, provided us a tool whose power is yet to be fully exploited in terms of targeted chemotherapy, and even fertility control. These are impressive examples of the social utility of basic science, and also of the patience needed for the practical development of beneficial measures based upon discovery of new fundamental knowledge.

"Discoveries in remote and unexpected fields" are the objective of the Government-university partnership. A concept expressed in the 1920s by Alfred North Whitehead characterizes our present effort. Whitehead said: "The proper function of a university is the imaginative acquisition of knowledge." I like to think that this concept can be applied to the function of NIH as well.[4]

An isolated fact is interesting but not useful until imagination places it in a larger context. At that point, as Whitehead said in the same lecture, "a fact is no longer a bare fact: it is invested with all its possibilities."[5] To be engaged in "the imaginative acquisition of knowledge" at this time is, in my opinion, the most exciting opportunity in the history of health science research.

But how shall we make sure that the momentum of scientific discovery is maintained? We have entered a phase of financial constraint in biomedical science. The period of explosive growth of the fifties and sixties, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. The second-stage rocket of the Cancer, Heart Disease, and Stroke initiative has

now played out. After reaching an all-time high in constant dollars in 1979, the NIH budget has leveled off, and in the past three years has declined about 12 percent in the same dollars. NIH is now a mature agency competing with other Federal programs for its share of the budget.

In the context of the present economy, NIH has been well treated by the Administration and the Congress, but it cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new steady state that all of us, NIH and universities alike, would do well to view as the future norm. A number of painful adjustments will be necessary if we are to secure the greatest amount of the best science within our available resources. Since it may not be possible to continue all the efforts and programs we have come so passionately to cherish, we will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration. Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term

advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds for the most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period.

The third principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between research productivity and the availability and replenishment of the supply of qualified investigators.

How well is the enterprise working, and what can be foretold of the future? What are the stresses on the system? What are the immediate concerns and the long-term problems?

I mentioned earlier that support of basic research is a responsibility of Government. This tenet has been explicitly reaffirmed by the Reagan Administration. In the case of basic biomedical research, which is conducted mainly in university laboratories, the bulk of support will continue to come from the Federal Government, primarily through NIH. In 1981, for example, 78 percent of health R&D funds used by universities came from the

Federal Government; 19 percent from university, state, local, and other nonprofit sources; and only 3 percent from industry. While industry has an important role in the continuum of health science research, its emphasis is chiefly on development and application. The primary search for basic knowledge will continue to be conducted by universities and national laboratories, with Federal dollars.

During most of the history of NIH, about four-fifths of the agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. Figure 1 shows that the percentage distribution of these funds among various types of institutions has remained fairly constant over the past ten years. For FY 1982, extramural awards amounted to $2.9 billion, 81 percent of the NIH budget (Figure 2). As shown in Figure 3, 52 percent of extramural support went to academic health centers such as this one at Emory University School of Medicine. These health centers have a national resource for which there is no substitute--your faculties of trained basic and clinical scientists. And further, one of your central purposes is to ensure the continuing renewal of that precious resource--the trained investigator.

I mentioned earlier that in my judgment the budget for biomedical research, more specifically the budget of NIH, could not be expected to grow substantially in constant dollars in the immediate future. But it is a very large budget, about $3.6 billion in FY 1982, and tending toward $3.9 or even $4.0 billion in FY 1983. The difficulty is that existing commitments from

award decisions of previous years have restricted flexibility in making new awards. NIH has been forced to examine and order its priorities much more carefully than during its two great periods of growth, which I have described as the Shannon era of 1955-68, and the Cancer, Heart Disease, and Stroke period of 1971-79. Budget constraints have led to a policy of stabilization, under which investigator-initiated research projects and research training have been given top priorities. In order to stabilize essential research programs, and to reduce the turbulence of the system, NIH has endeavored each year to fund a minimum of 5,000 new and competing renewal awards, and to support a minimum of 10,000 trainees. I would like to address the matter of research grants first, and defer until a little later any further reference to training.

NIH succeeded in funding about 5,100 new and competing awards in FY 1981, and 5,030 such awards in FY 1982, which ended on September 30. The latter number is almost 300 awards greater than the predicted figure of 4,741. The increase was achieved by budgetary shifts (about which more will be said in a moment), downward negotiation of the size of awards, and assignment of virtually all year-end dollars recaptured from unexpended awards of whatever category to the funding of new research grants. During both FY 1981 and FY 1982, 50 percent of our budget went into the support of investigator-initiated grants (Figure 4).

The stabilization policy makes a powerful statement to the extramural community. It says that NIH is doing its utmost, consistent with program balance and congressional mandates and

directives, to assure that the best research will be adequately funded, and that young scientists will have opportunities in research; that we will protect their entry into the research enterprise, not out of charity but because the vitality of the enterprise--the success of the research endeavor--depends on them. In both 1981 and 1982, 50 percent of all new research grant awards went to principal investigators who were first-time applicants. This number represents 12 percent of our total portfolio of about 16,000 grants.

But the stabilization policy also has its down side. In order to fund 5,000 new and competing projects, dollars have been shifted from other mechanisms for the past 3 to 5 years (Figure 5). While the proportion of the NIH budget assigned to support investigator-initiated research projects has grown from 39 to 50 percent, other mechanisms have been curtailed, especially contracts, centers, and clinical trials. After several turns of the ratchet, many Institute Directors feel that further shifts would seriously limit their abilities to meet other program goals and to maintain program balance.

The President's 1983 budget for the NIH requested $108 million above the 1982 level. Because of commitments that carried forward, in the absence of other adjustments the 1983 budget would have permitted funding of only 3,200 new and competing awards. In order to raise this number, further shifts were accepted by the Institute Directors and, in addition, NIH proposed to fund the institutional allowance on training awards at about 50 percent of customary levels, to reduce payment of

noncompeting awards by an average of 4 percent, and to pay indirect costs only to the extent of 90 percent of negotiated rates. These "savings," taken together, will permit funding of about 900 additional awards, raising the anticipated number for 1983 to 4,100.

During 1982, although we funded 5,030 new and competing awards, this figure represented only about a third of the approved grants (Figure 6). The priority scores of those funded cut off at 160-180 in most cases (Figure 7). Although these pay rates and pay lines are the lowest in NIH history, the figures are not quite as grim as they might at first appear to be. Both are influenced by "grade inflation." This slide also shows that priority scores of approved grant applications have dropped somewhat since 1980 (left panel), and of funded projects rather sharply since 1979 (right panel) when the NIH budget began to decline in constant dollars (Figure 8). Prior to 1976, 60-70 percent of new applications and 85-90 percent of competing renewals were approved by study sections. In 1982, comparable figures were 80 and 94 percent and these higher approval rates in part explain why a smaller percentage of the approved grants can actually be awarded. When the same data are expressed as "success rates," meaning the percentage of submitted grant applications that are funded, current and historical figures compare more favorably. Nevertheless, many strong, potentially productive, and valuable research projects are presently excluded by the stringency of the budget. Excellent established investigators as well as well-qualified newcomers are being denied support.

One of our critics has described the current situation as the Matthew 25:29 phenomenon: "For unto every one that hath shall be given, and he shall have abundance: but from him that hath not shall be taken away even that which he hath."

The anxiety in the research community has led to varied responses, in my view largely constructive. In public testimony and private correspondence they have impressed upon the Congress the need for additional funds for biomedical research. Both the House and Senate appropriations committees have added funds to support a total of 4,900-5,000 new and competing awards. These bills have yet to reach the floors of the two chambers, but the portents are encouraging.

But not all responses have been constructive and some, though as yet quantitatively minor, bode ill for the future if they should become common practice. Let me cite two examples. A few investigators are sending their new grant applications simultaneously to NIH and to their Congressmen and Senators. In one instance, we received a congressional inquiry as to why an obviously meritorious and important research project had not been funded, only to learn that the Congressman had received his copy of the application before we did. A second example involves a new category of awards that we have termed "disapproved, but funded." We now have several examples of grant applications funded by specific congressional mandate after they had received too low a priority to be funded, or had been disapproved altogether.

Some scientists have attacked the fundamental integrity and equity of the peer review system. It is a human system, and no one would contend that its judgments are flawless. It has operated with very little criticism for thirty years. There always has been a cutoff point below which grants could not be paid due to limitation of funds. However, the quality of applications at the margin differs considerably when the payline is 160 rather than 260, and unrest in the extramural community is correspondingly higher. The only way to avoid the problem altogether is to be able to pay all approved grants, and this utopian day is unlikely ever to arrive. Applicants whose priority scores fall outside the payline are provided information on the shortcomings of their application and have the option of rewriting their material and resubmitting. In the last round of grants reviewed by the NIH, 23 percent of all grant applications received were resubmissions. There is also an appeal mechanism for any applicant who feels that he or she has not been dealt with fairly.

Others have suggested a limitation of the dollar support awarded to any individual principal investigator. This proposal has taken several forms. One is to limit the number of dollars per project or per laboratory. Another is to limit the number of grants in the name of any principal investigator. At present about 10 percent of principal investigators have two or more grants, although frequently the second is a training grant or a salary award. Since the NIH supports projects rather than laboratories or individuals, we are only permitted to ask

questions regarding additional support available for the project under review. Thus our information on the total financial support of any principal investigator or laboratory is incomplete, and without such information we would have difficulty in dealing equitably with either of these mechanisms. A third mechanism, which has received far greater support, is a sliding scale in the payment of approved awards. It is suggested that NIH fund grants of the very highest priority scores at 100 percent of the award rate, the next lower category at 90 percent, followed by 80 percent, 70 percent, and so on. We have examined this concept very carefully but find it flawed in several particulars.

At present, the recommended level of support of grants approved by study section averages 18-20 percent less than the requested amount. The actual award rate is further negotiated by the extramural grants management division, and currently averages about 8 percent below the rate recommended by the study section. The severity of downward negotiations both by study sections and grants management specialists roughly parallels the priority score. In other words, those grants with the highest priorities tend to be paid in amounts closer to the requested budget than those with somewhat lower scores. Thus there are within present practices some features of the sliding scale philosophy.

But we are reluctant to formalize the sliding scale mechanism or to apply it mechanistically. In our view, such a practice would fund many projects inadequately and would result in waste of taxpayers' money. It would reduce the average cost

per project, and since this is one of the factors in the construction of budget requests to Congress, such a change would have the self-defeating consequence of reducing subsequent NIH budgets and of making it impossible for us to fund as many grant awards the following year.

As we have reviewed these alternatives for spreading research dollars across a larger number of investigators, we have reaffirmed the traditional practice of awarding grants on the dual bases of scientific merit and program relevance, as determined by study section and council review. Some years ago Philip Handler, former President of the National Academy of Sciences, stated in congressional testimony: "In science the best is vastly more important than the next best."[6] Jay Keyworth, the President's Science Advisor, has characterized science as "an unabashed meritocracy."[7] John Gardner, in his book on Excellence, asks: "Can we be excellent and equal too?"[8] While we share a deep concern for scientists whose deserving projects we cannot fund, we think that the interests of science are best served by funding the most meritorious work as judged by the peer review system, and by assuring that such projects are funded parsimoniously, yet adequately for the execution of the study.

A second major arena of vigorous response to the President's 1983 budget has been the proposal to pay only 90 percent of the negotiated rate of indirect costs on NIH research grants. Let me define the problem as it is seen by NIH. Prior to 1966, NIH paid a flat rate of 15 percent of the total award to cover indirect

costs of a project. The Wooldridge Report of 1966 recommended that NIH abandon the flat rate, and instead pay a negotiated rate of indirect costs based on audits of actual expenditures.[9] For the next six years the average indirect cost rate rose rapidly, and by 1972 amounted to 24.2 percent of the total research dollar (Figure 9). Since that time it has risen less sharply but at a steady rate of 0.53 percent per year. In FY 1982 it reached 30.0 percent of the total grant dollar.

This inexorable rise of the total fraction of the research budget represented by indirect costs has occurred irrespective of the rate of change of the research budget itself. The linear increase is the same during the expansion of the NIH budget resulting from the Cancer, Heart Disease, and Stroke initiatives as during the constriction of the budget since 1979. In FY 1982, the budget of the NIH for awards and contracts increased $52 million. Of this, $29.1 million, or 56 percent, was consumed by indirect costs. In virtually every one of the last 16 years, the indirect cost rate has grown faster than the direct cost rate.

The issue has been raised to a high level of visibility by the responses of university administrators to the Congress. The administrators are understandably concerned about the solvency of their institutions, and emphasize that indirect costs are true costs of research, a point we do not contest. In the current continuing resolution Congress has temporarily provided additional funds for full payment of indirect costs. However, Congress is also concerned about the rate of growth of indirect costs. In its report on the proposed 1983 budget, the House

Committee on Appropriations has asked for two studies of indirect costs, one by the Department of Health and Human Services, another by the Government Accounting Office. At issue are the containment of indirect costs, and the extent of cost sharing between the universities and the Federal Government. This has become a divisive issue which requires early resolution. The present proposal of paying only 90 percent of negotiated rates has the unfortunate consequence of penalizing those schools that have kept indirect costs low as well as those that have not. Such a proposal is clearly not a long-term solution, and indeed was proposed only as an interim device. I anticipate that a satisfactory resolution of this matter will be developed within the next year.

To this point I have outlined the fundamentals of our approach to the support of medical research by NIH and to the current policy of stabilization, which gives top priority to investigator-initiated research projects. I would now like to raise a subject of special concern, namely the present and future state of clinical research. A burgeoning of basic knowledge in the past decade has opened up vast opportunities for clinical research; nevertheless, diminishing numbers of physicians are interested in applying themselves to the clinical research needs of tomorrow.

Some quantitative data may serve to emphasize the points to be made. Figure 10 shows the number of principal investigators on all research project grants holding M.D., Ph.D., or combined M.D. and Ph.D. degrees, as these have varied during the past

dozen years. Notice the decline in the number of M.D. investigators from about 3,400 in 1968 to about 2,500 in 1973. Since that time the number has increased slightly but in 1980 was still below 3,000. The number of Ph.D. investigators has always been somewhat greater than of M.D. investigators. It declined slightly from 1968 to 1973, but since that time has displayed an almost linear growth. When these data are expressed as a percentage of all principal investigators on research grant awards, as in Figure 11, they describe a rather steady decline in the percentage of grants held by M.D. investigators from about 35 percent of the total in 1968 to about 23 percent in 1980.

During the same time span the percentage of grants held by Ph.D. investigators increased from 52 to 67 percent. The percentage held by M.D.-Ph.D. investigators has remained nearly steady at about 10 percent of the total. The decline in the number and percentage of M.D. investigators reflects to a large extent the submission of fewer grant applications by M.D. than Ph.D. scientists. The approval and award rates for competing research grant applications did not differ greatly for M.D. and Ph.D. applicants between 1974 and 1980.

Figure 12 shows a table of such rates for all competing awards, including both new and renewal applications. The approval rate for applications submitted by Ph.D. investigators has run 4 or 5 percentage points ahead of rates for M.D. investigators. But of the grants approved by study sections, the award rates for M.D. and Ph.D. principal investigators have been virtually the same.

When one looks at the success of new applicants alone (Figure 13), one finds that since about 1974 new M.D. applicants have competed somewhat less well than new Ph.D. applicants, and that both groups have competed less successfully than M.D.-Ph.D. applicants. This trend is even more dramatic when expressed in comparison with the average success rate of all research grant applications of that year, which in Figure 14 has been given a score of 1.0. Note that increasingly the greatest success is obtained by the M.D.-Ph.D. applicant, followed by the Ph.D. applicant at somewhat above the average rate, and by the M.D. applicant, who is increasingly below the average rate. The disparity of success rates of M.D. applicants is even more impressive in the subfraction of M.D.-authored grant applications that constitute clinical research in its most specific form, namely research that requires the doctor-patient relationship in its performance.

Figure 15 tabulates the shortcomings of poorly rated or disapproved NIH grant applications. These data apply to the entire spectrum of grant applications. An analysis of the reasons why grants submitted by M.D.s fail, in particular those involving clinical research, shows that the shortcomings follow the same profile of causes as those of the pool in general. Most such grants fail because of a faulty hypothesis, or some flaw in experimental design, most commonly in technical methodology. Rejections because of inadequacy of investigator are no more frequent in the case of M.D. investigators than for the entire pool.

In his Presidential Address to the Association for American Physicians in May 1982, John Oates documented the correlation between the success rate of physician applicants for research support and the length of training of the applicant.[10] The success rate was poor with less than two years of postdoctoral research training; but it was better after three or four such years than after two.

In my view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science. Clinical research requires experiences not represented in most medical school and house staff experiences. The quality of a research grant application is a reflection of the competence and sophistication of the investigator applicant. As Damon Runyon said, "The race is not always to the swift or the battle to the strong, but that's the way to bet."

The clinical investigator provides the indispensable link between the laboratory and the human being, who is the ultimate focus of all our endeavors. For this reason we view with great concern the decline in the number of M.D.s in NIH-supported research training programs from 4,500 in 1971 to about 1,800 in 1981 (Figure 16).

When NIH research training programs were modified in 1974 under the National Research Service Awards Act, to provide training exclusively for research or academic development, a committee of the National Academy of Sciences recommended that 2,800 clinical research training slots be offered annually, 2,400 as traineeships and 400 as direct fellowships. This figure of 2,800 clinical training positions was not reached until 1980, but at that time 900 of the traineeships were held by Ph.D.s, and only 1,900 by M.D.s. The Academy committee has recommended that at least 85 percent of the traineeships in this category be filled by M.D. candidates. And so by every yardstick, we are failing to attract the number of physicians perceived to be desirable by the Academy committee, and this bodes ill for the balance between M.D. and Ph.D. investigators deemed essential for coordinated progress in basic science and clinical research.

Many reasons have been cited for the declining interest of physicians in clinical research. Most medical school curricula provide little or no laboratory experience that is representative of modern day biomedical science. The rise of specialty fields and the lengthening of postdoctoral training programs have extended the clinical training necessary for board certification. The requirements of many certification boards are rather inflexible and certainly do not encourage the potentially creative physician to enter research training. The payback provision of the National Research Service Award has acted as a deterrent for some potential traineeship applicants. Perhaps dominating the issues is financial disincentives: the average

gap between the previous year's residency salary and the first-year traineeship is now $4,500; differences between income possibilities in research and in procedure-oriented practices of medicine are very much larger. When the medical student's debt load at graduation is frequently $20,000 or more, the cumulative financial disincentives are a major factor in dissuading potential investigators from entering the field.

Fortunately this growing problem has received considerable attention in the Congress. Just a few weeks ago we received the Report of the House Committee on Appropriations regarding the proposed 1983 budget for the National Institutes of Health. Permit me to read a paragraph.

> "The Committee shares the concerns that have been expressed by official and public witnesses about the difficulty of recruiting and retaining physicians for research careers, especially as all clinical research, involving human patients must be done by--or, at least, under the guidance and supervision of--a qualified physician. It is apparent and understandable that young physicians considering careers in health research are often dissuaded from applying for research training or research fellowships by their perception of instability in the Federal commitment to research and by their awareness that a research career represents a substantial financial sacrifice when compared with almost any form of medical practice. The Committee would like NIH to review this problem carefully and to

suggest what steps might usefully be taken to increase the number of young physicians who will apply for research training and to retain those who do embark on research careers. The Committee will expect a report on this subject at next year's hearings."[11]

Even without that prodding, we have devoted considerable attention to this problem and have under consideration some major steps toward its solution. You may be sure that the preparation of this report will receive our most careful attention.

In the portion of its report preceding the statement on clinical research, the Committee explained its decision to increase the appropriation requested for all research training programs by over $18 million to provide for a total of 10,000 trainees--a level perceived by the Committee as barely large enough to balance the inevitable attrition.

NIH has already taken some steps to alleviate this shortage and is considering others. At the undergraduate medical student level, we have continued to give the Medical Scientist Training Program top priority in our training portfolio. This year we will support about 650 students in programs leading to combined M.D. and Ph.D. degrees. The NRSA permits short-term training of medical students for up to three months per year. This past year, over 900 medical students availed themselves of such off-quarter training opportunities supported by NIH. With exemption of the first year of NRSA support from payback obligation, NIH can now reinstitute the post-sophomore fellowship or its

equivalent, and thus provide a full year of research training within the medical school experience under an NIH fellowship or traineeship. NIH also offers summer research fellowships at Bethesda, and during this past year about 50 medical students participated in that program.

In order to maximize the opportunities for young physicians to secure research training, NIH has requested appropriate review bodies to give M.D. applicants special consideration in the award of research fellowships, and has advised clinical research training program directors to give first priority to M.D. applicants before appointing Ph.D. trainees to the available slots. NIH is considering other measures that might restrict the number of clinical traineeships offered to Ph.D. applicants along the percentage guidelines suggested by the National Academy of Sciences. But the disparity between residency and fellowship stipends remains a serious problem. Within the next few weeks we will be discussing possible mechanisms for closing this financial gap, but adjustments adequate to achieve this goal will probably require congressional approval.

NIH also faces some longer-term problems that must be addressed in the interest of the health and vitality of the research enterprise. When the economy improves, an increase in funding for scientific research and development is clearly indicated if we are to maintain our position of leadership in the world. This statement is just as true for other areas of science as it is for biomedical research. We also need to address the issues of obsolete equipment and research facilities, which in

the case of medical science now often include buildings constructed 20-25 years ago.

But no one attending the Herndon lecture needs to be persuaded of the importance of biomedical research to society or to the academic health center. Examples abound to document the relief from suffering that has resulted from the application of research advances. In addition, students, faculty, and others can readily appreciate how the curiosity and critical inquiry of research enhance the teaching and health care environment in an institution such as this. Engraved at the entrance to the NIH Clinical Center auditorium is a quotation from its first Director, Dr. Jack Masur, for whom the auditorium is named, that beautifully captures this concept: "Hospitals with long traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching, teaching lifts the standards of service, and service opens new avenues of investigation."

Thank you very much once again for the invitation to inaugurate this lectures series, and for your interest and attention this afternoon.

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8. Gardner, J. W. Excellence: Can We Be Equal and Excellent Too? New York: Harper and Row, 1961.

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10. Oates, J.A. Clinical Investigation: A Pathway to Discovery. Address before the Association of American Physicians, May 1982.

11. United States, 97th Congress, second session, 1982. House Report 97-894: Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriation Bill, 1983, p. 28.

Lecture
Figures for Herndon ~~Speech~~, 12/13

Figure 1. NIH Extramural Awards by Kind of Institution, Fiscal Years 1972 and 1982.

Figure 2. Extramural Awards Make Up 81% of NIH Budget, Fiscal Year 1982.

Figure 3. Medical Schools Receive 52% of all NIH Awards, Fiscal Year 1982.

Figure 4. Council Recommended for Approval and Award Rates for Number of NIH Research Project Applications by Type, Fiscal Years 1972-1982.

Figure 5. Allocation of NIH Extramural Awards by Activity, Fiscal Years 1972-1982.

Figure 6. NIH Budget, Fiscal Year 1982.

Figure 7. Number of NIH Competing Research Project Applications Reviewed, Eligible, and Awarded, Fiscal Years 1972-1983.

Figure 8. Priority Score Trends for NIH Competing Research Projects, Fiscal Years 1976-1982.

Figure 9. Indirect Cost Percentage of Total Cost for NIH Research Grants, Fiscal Years 1972-1982.

Figure 10. Number of P.I.'s on All R01 Grants Holding MD, PhD or Md/PhD Degrees.

Figure 11. P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants.

Figure 12. Approval and Awards Rates for Competing R01 Applications, 1974-1980.

Figure 13. Success of New Applicants on NIH Research Projects (Type 1 R01 Applicants by Type of Degree of P.I.)

Figure 14. Success Rates of New MD, PhD, and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year.

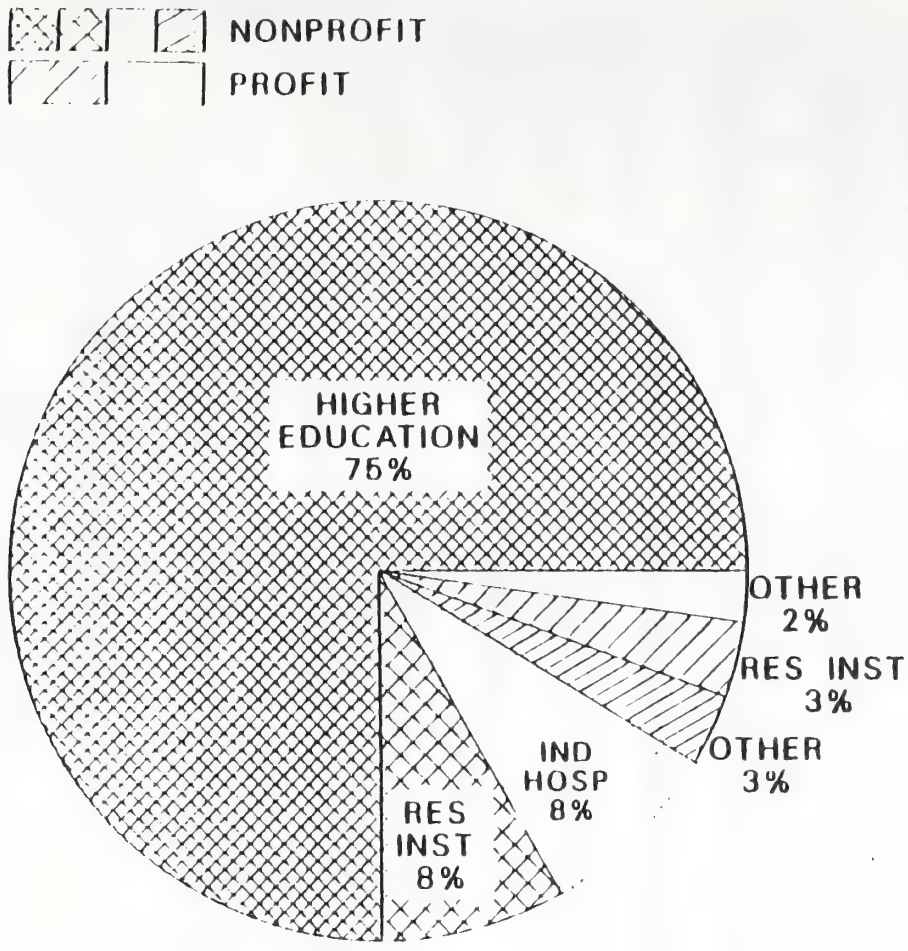
Figure 15. Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications.

Figure 16. Trainees and Fellows on NIH Research Training Awards, 1971-81.

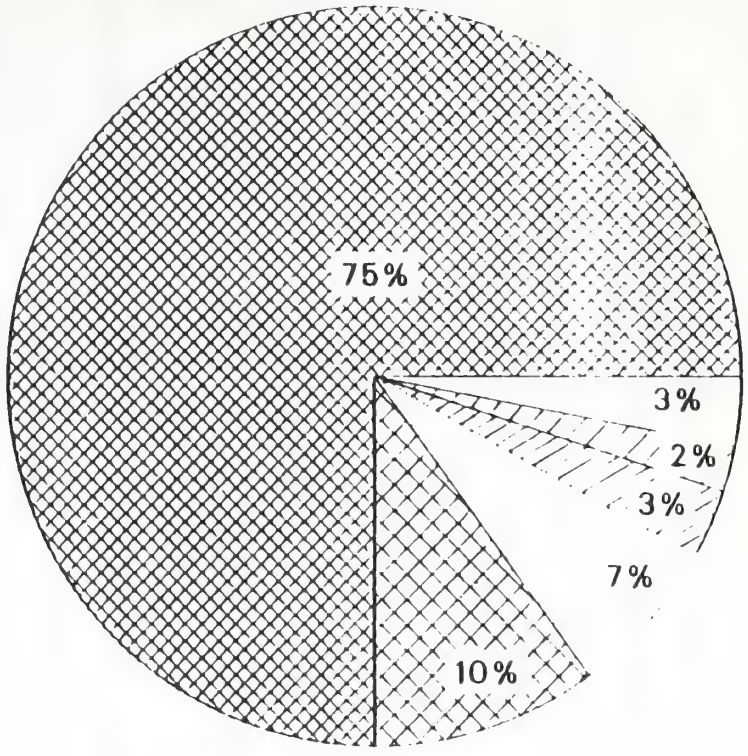
CHANGE IN TEXT

Insert A, page 10. Figure 1 shows that the percentage distribution of these funds among various types of institutions has remained fairly constant over the past ten years. For FY 1982, extramural awards amounted to $2.9 billion, 81 per cent of the NIH budget (Figure 2). As shown in Figure 3, 52 per cent

[illegible] AWARDS BY KIND OF INSTITUTION, FISCAL YEARS 1972 AND 1982
(CURRENT DOLLARS)



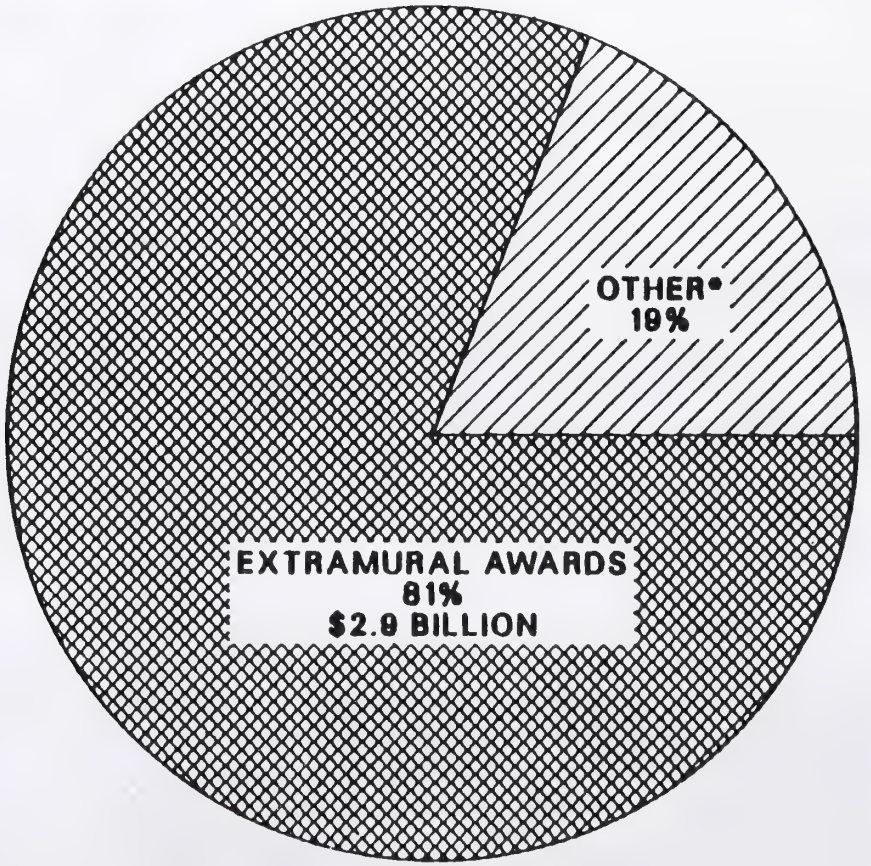
FY1972
$1,254 MILLION



FY1982*
$2,933 MILLION

*PRELIMINARY
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET
FISCAL YEAR 1982

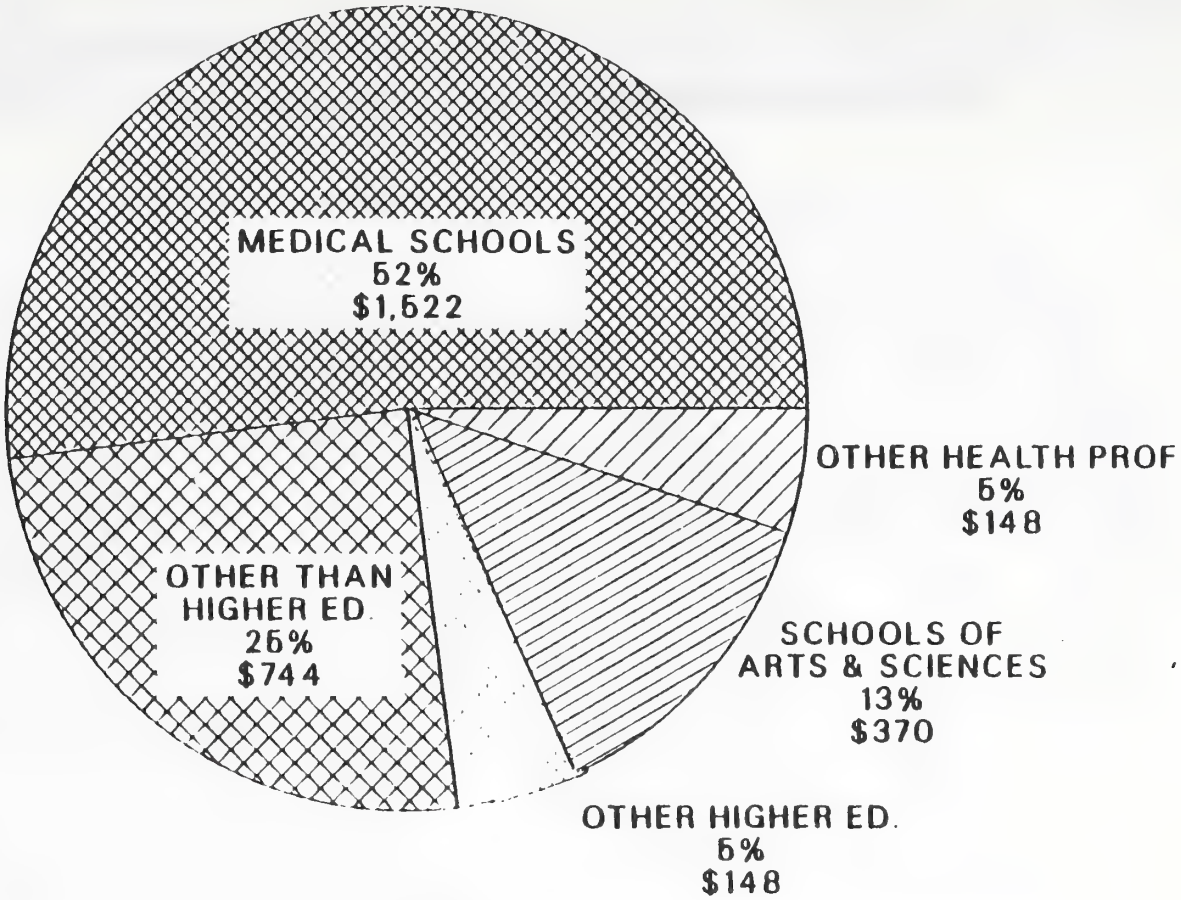


TOTAL - $3.6 BILLION

*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



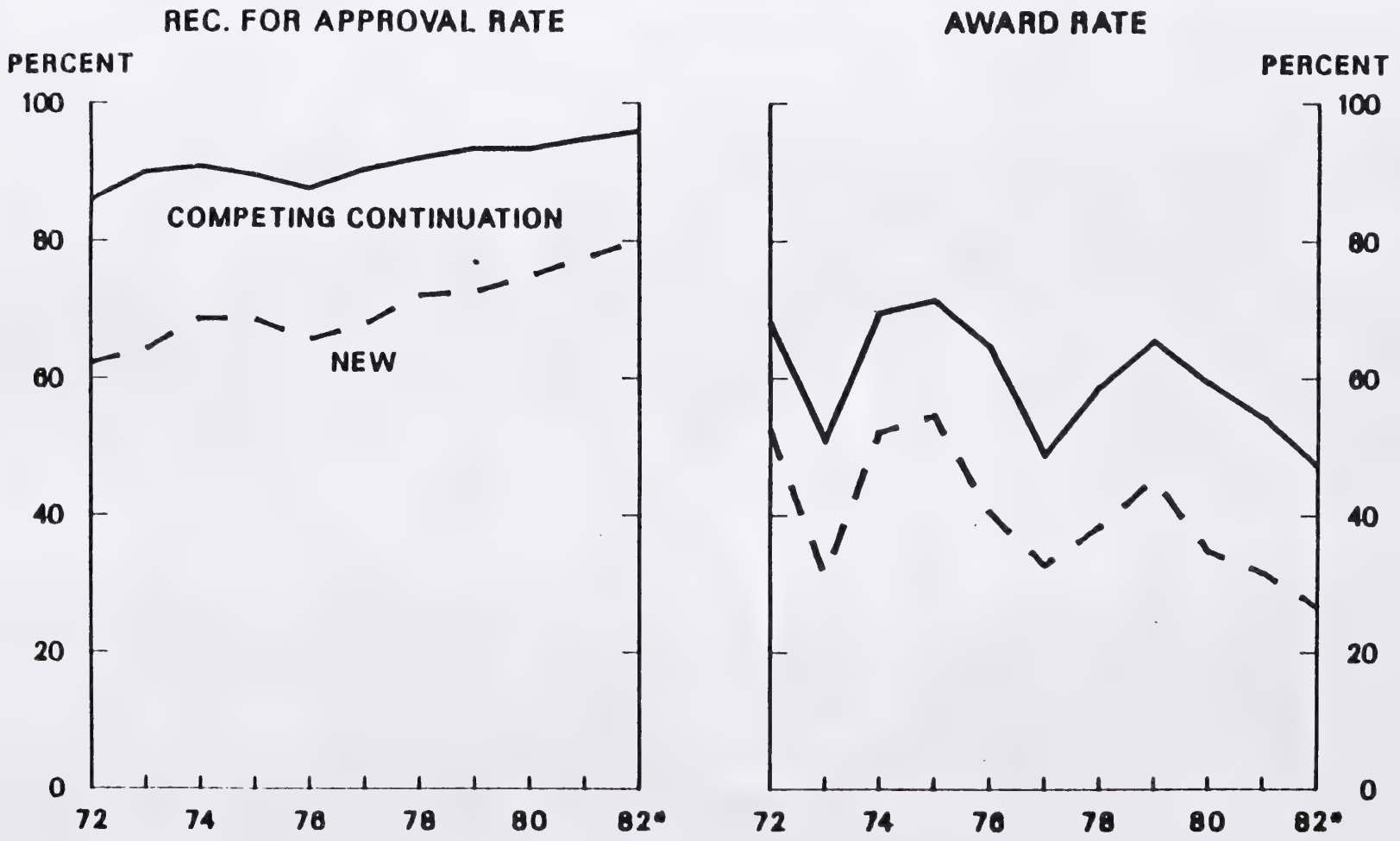
FY 1982*

$2,933 MILLION

*PRELIMINARY
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

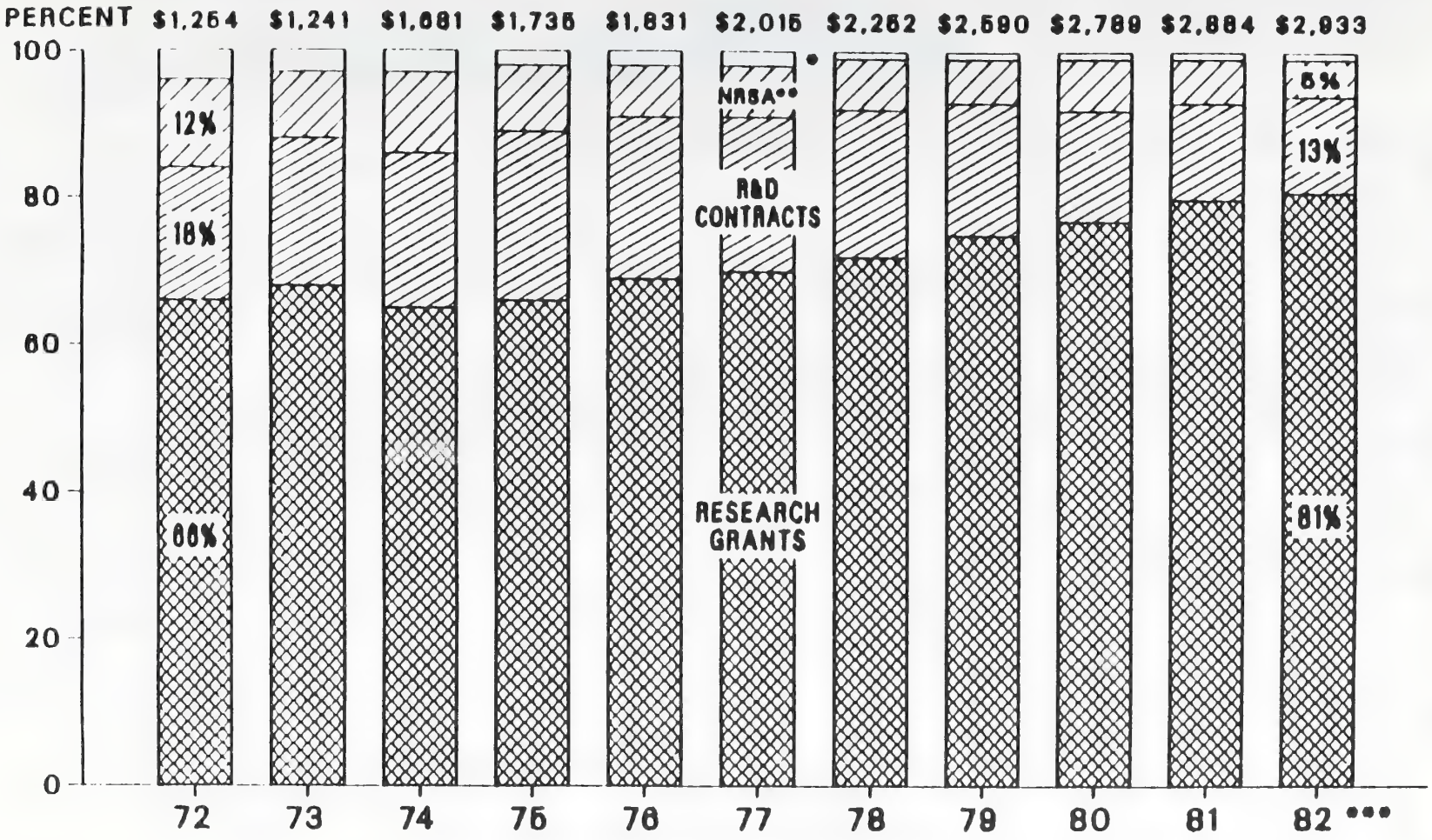
(4)

COUNCIL RECOMMENDED FOR APPROVAL AND AWARD RATES FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS BY TYPE, FISCAL YEAR 1972-1982



NOTE: DATA BASED ON NIH STANDARD PROCEDURES. *PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

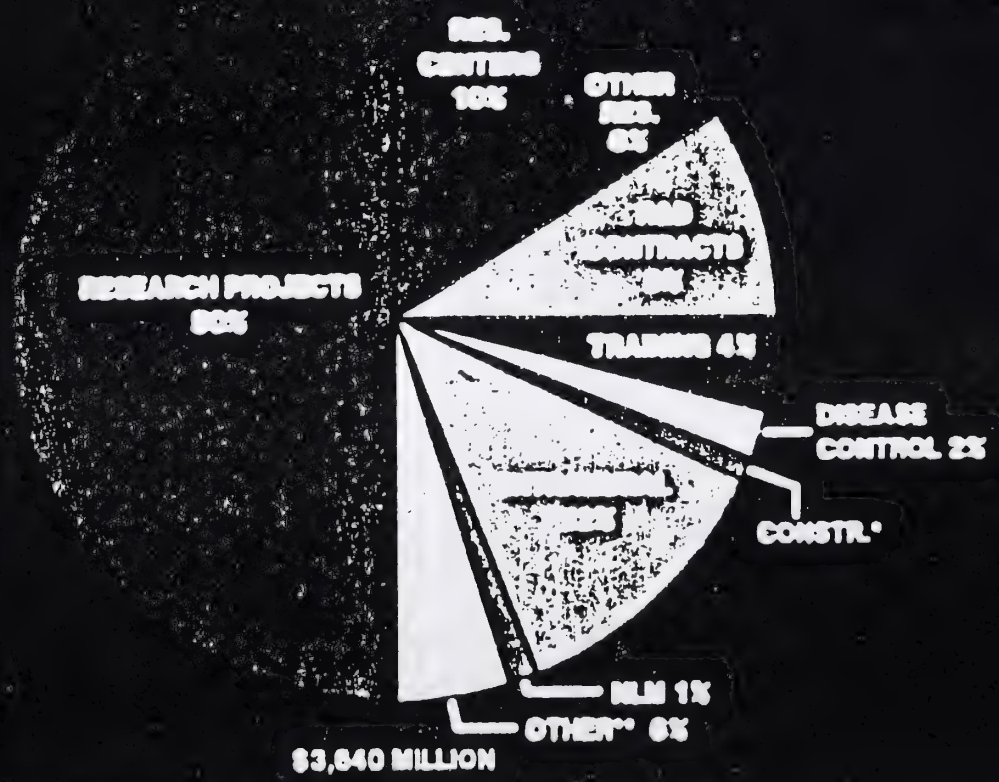
ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE: EXCLUDES TQ. *INCLUDES CONSTRUCTION, CONTROL, AND MEDICAL LIBRARY GRANTS.
**INCLUDES PRE-NRSA TRAINING. ***PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

NIH BUDGET, FISCAL YEAR 1982

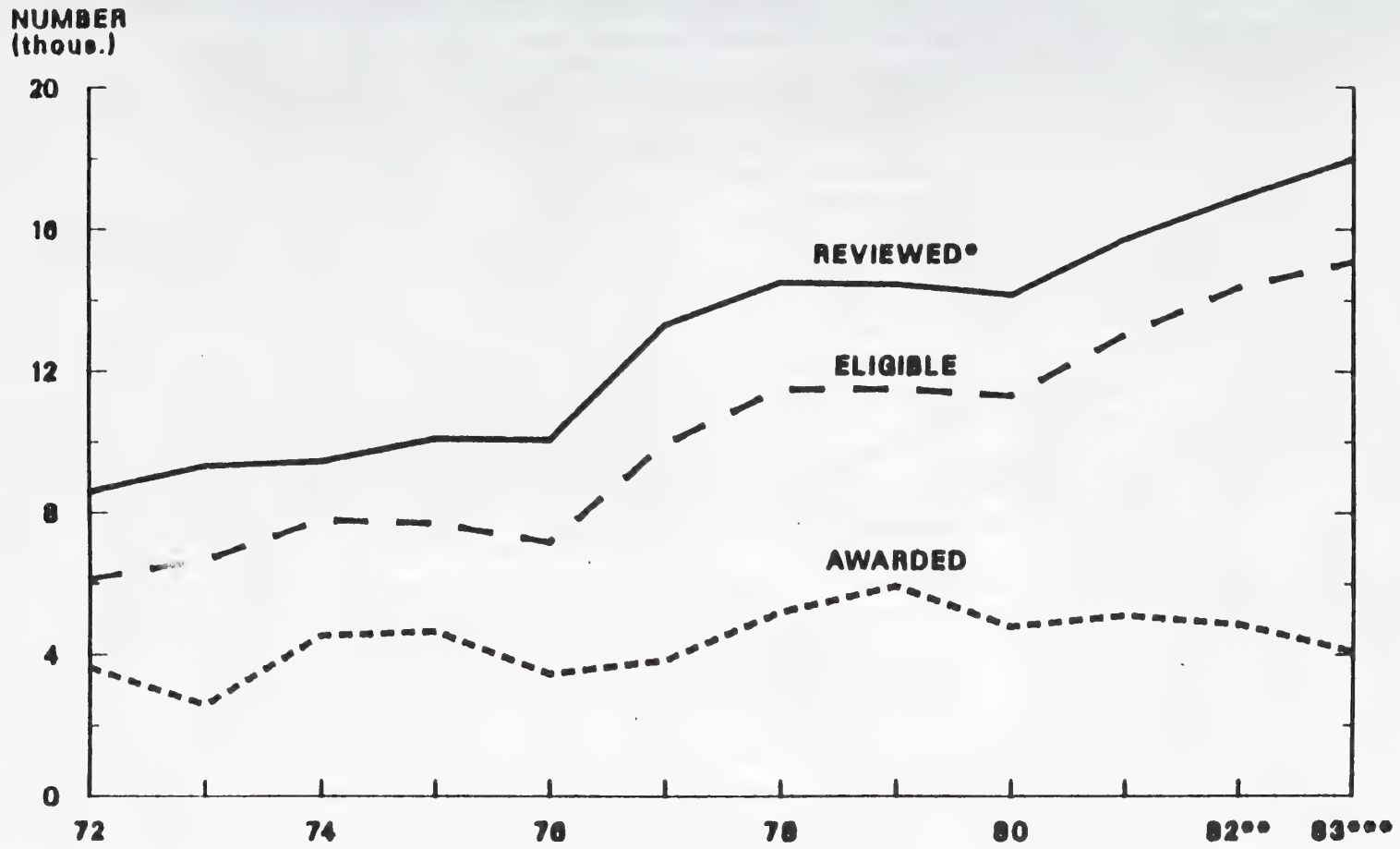
(CURRENT DOLLARS)



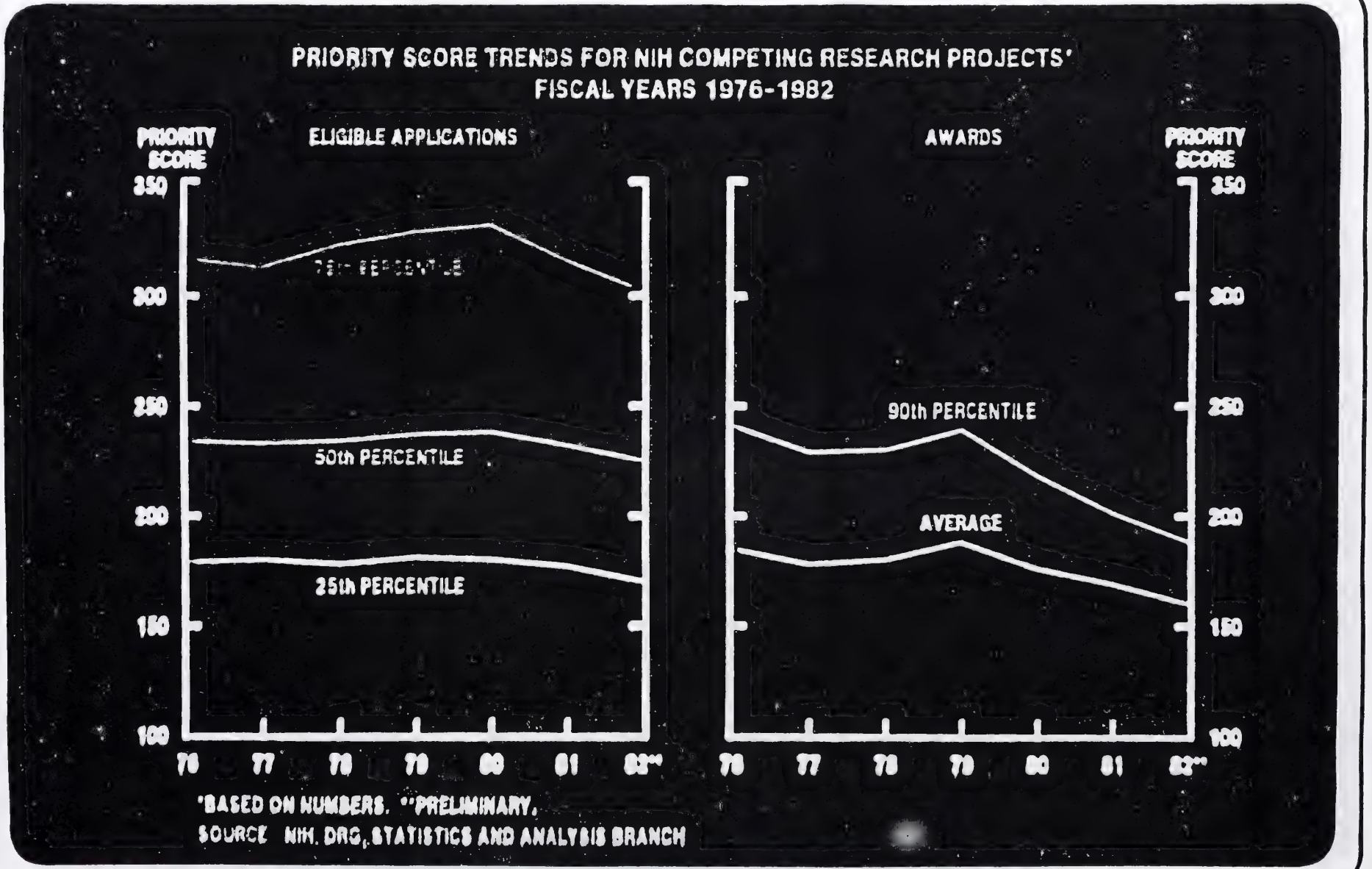
* LESS THAN 1%. ** ADMINISTRATIVE SUPPORT, BUILDINGS, AND MANAGEMENT.

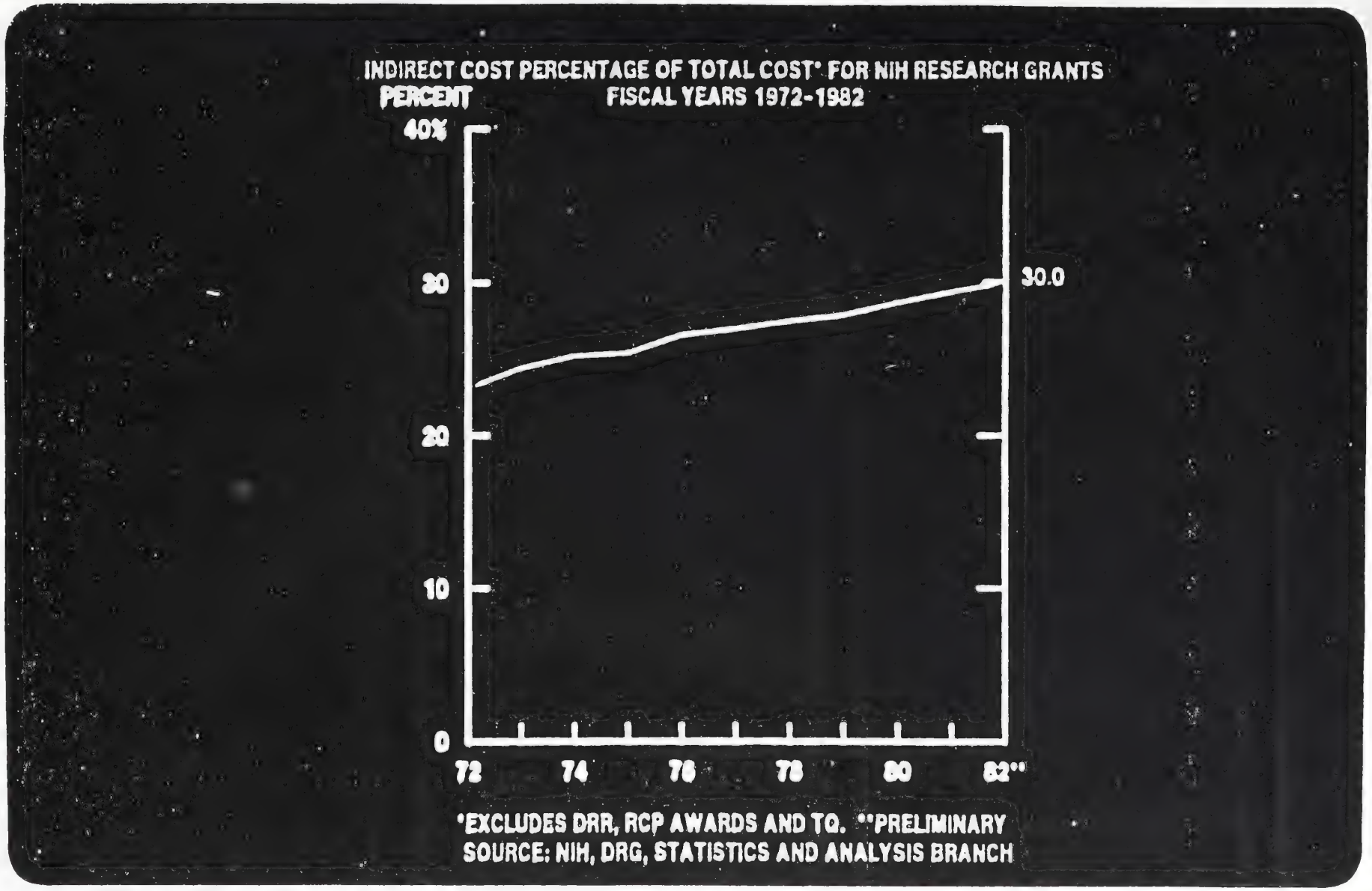
SOURCE: BFPB, DFM, 1982 COLUMN OF 1984 PRELIMINARY TO NIH, DATED 4/20/82, (PREPARED BY DRG, SAB).

NUMBER OF NIH COMPETING RESEARCH PROJECT APPLICATIONS REVIEWED, ELIGIBLE AND AWARDED, FISCAL YEARS 1972-1983

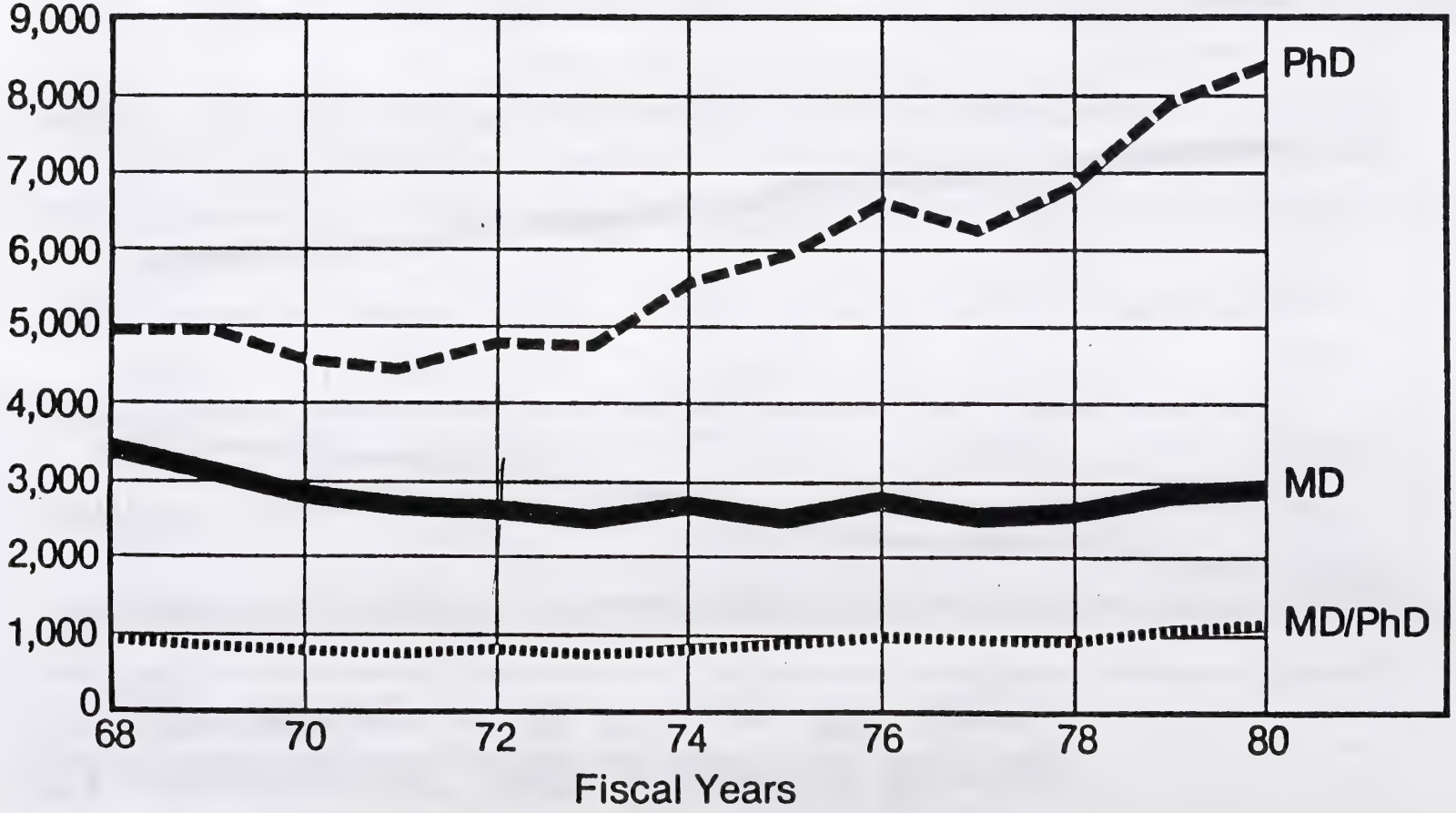


NOTE: EXCLUDES TQ. DATA BASED ON NIH STANDARD PROCEDURES. *REPORTING YEAR.
**PRELIMINARY. ***ESTIMATED.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

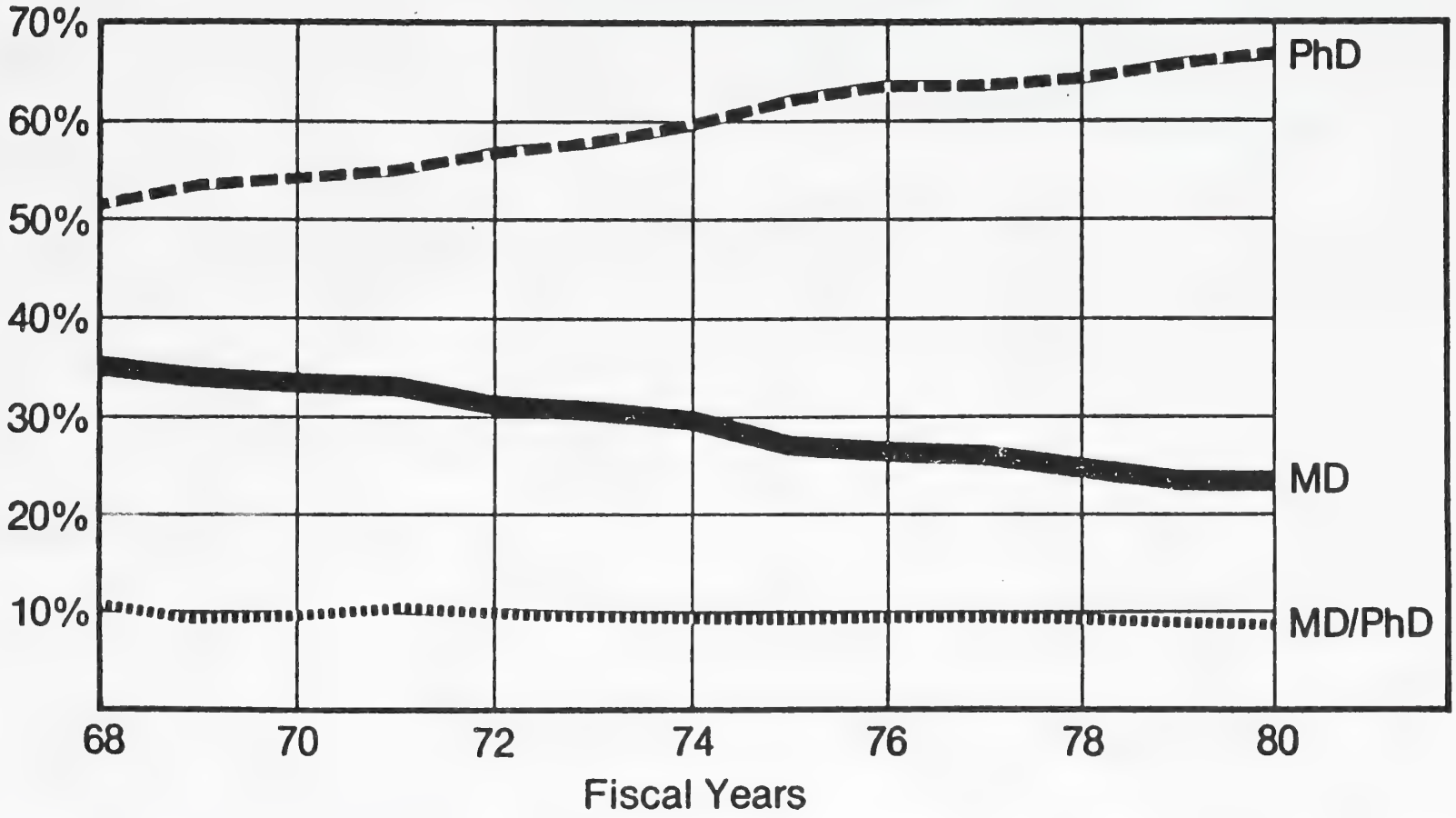

PRIORITY SCORE TRENDS FOR NIH COMPETING RESEARCH PROJECTS*
FISCAL YEARS 1976-1982
PRIORITY SCORE
ELIGIBLE APPLICATIONS
AWARDS
PRIORITY SCORE
350
300
250
200
150
100
90th PERCENTILE
50th PERCENTILE
25th PERCENTILE
AVERAGE
76
77
78
79
80
81
82**
*BASED ON NUMBERS. **PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH


INDIRECT COST PERCENTAGE OF TOTAL COST* FOR NIH RESEARCH GRANTS
FISCAL YEARS 1972-1982
PERCENT
40%
30
20
10
0
30.0
72
74
76
78
80
82**
*EXCLUDES DRR, RCP AWARDS AND TQ. **PRELIMINARY
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants



F:93

(1)

Approval and Awards Rates for Competing R01 Applications: 1974-1980

	Approval Rate		Award Rate	
FY	M.D.	Ph.D.	M.D.	Ph.D.
1974	73.9	78.9	60.7	56.0
1975	72.0	77.4	59.5	60.2
1976	67.7	73.8	50.4	47.2
1977	72.0	76.0	41.2	36.8
1978	74.4	80.2	44.1	45.5
1979	76.1	79.4	51.1	51.7
1980	76.7	81.0	41.5	41.7

Success of New Applicants on NIH Research Projects (Type 1 R01 Applicants by Type of Degree of P.I.)

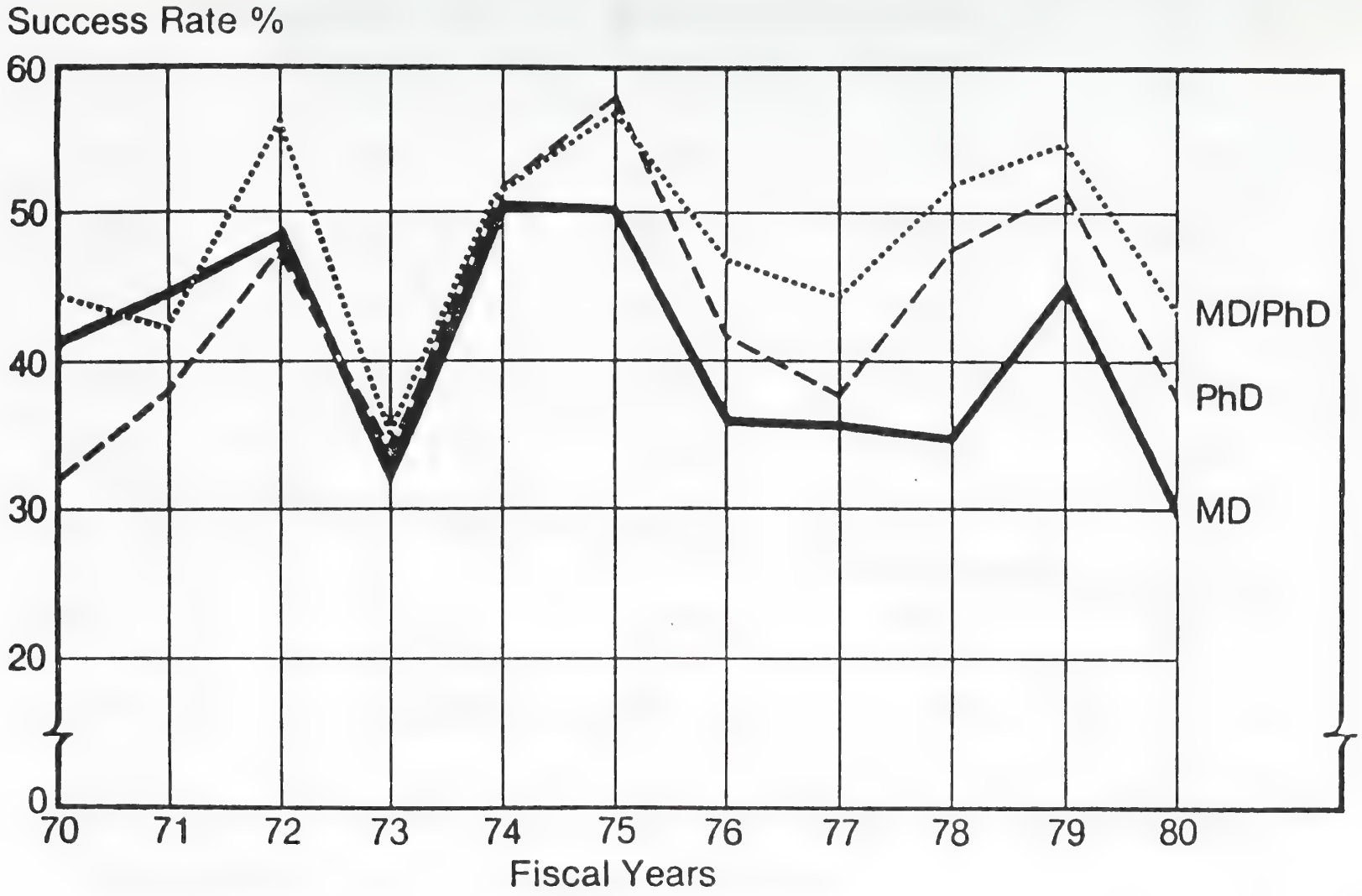
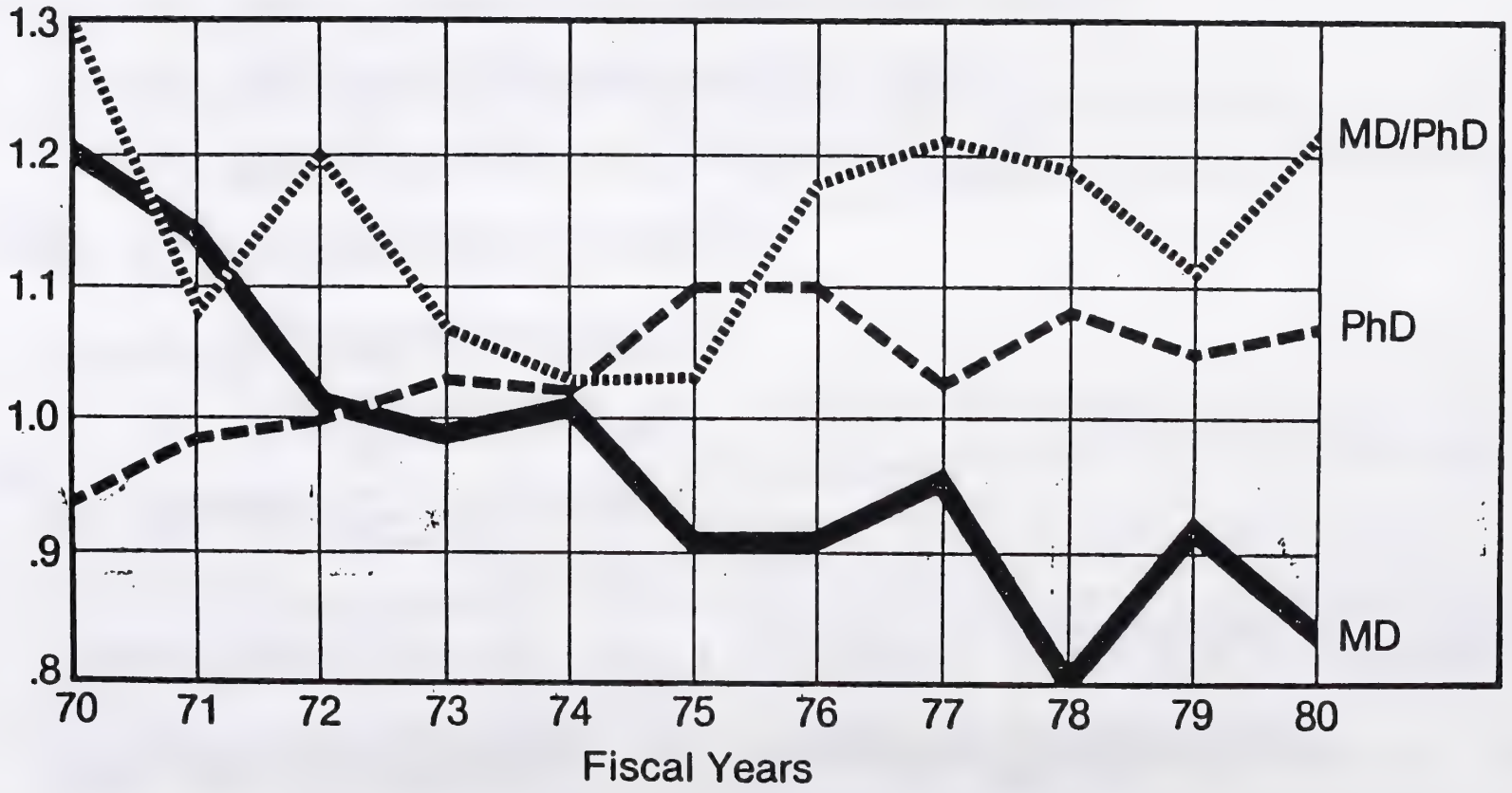


Fig 5

Success Rates of New MD, PhD and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year

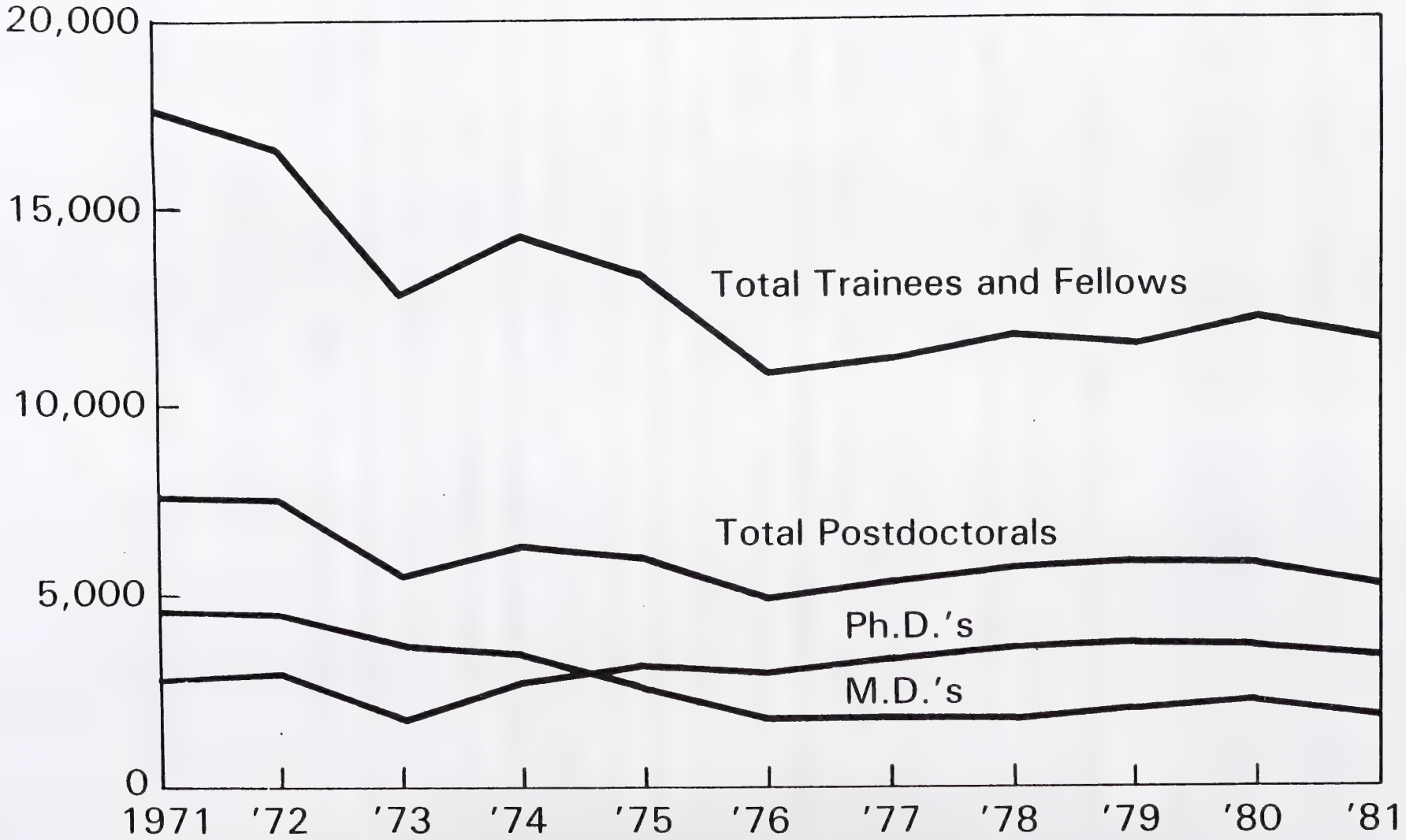


Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - — Hypothesis (47%)
  - — Significance (30%)
- Experimental Design:
  - — Study Group or Controls (40%)
  - — Technical Methodology (66%)
  - — Data Collection Procedures (41%)
  - — Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81

A-300



GOVERNMENT, INDUSTRY, AND ACADEMIA: A BERMUDA TRIANGLE?*

By

James B. Wyngaarden, M.D.**

In the Caribbean, as you know, there is a mythical area known as "The Bermuda Triangle." It is said that there is a mysterious force field in the area that swallows up those who enter. The story occurred to me as I thought about the government-industry-academia triangle involved in the research enterprise. Last evening, Frank Press reiterated how fraught with apparent risks the existing relationships are. He also cited the new report of the National Science Board entitled "University-Industry Relationships" and its subtitle: "Myths, Realities, and Potentials." Some of the issues raised by the new university-corporate arrangements being formed to pursue research are as mythical as the Bermuda Triangle, others are real, still others are of ambiguous potential.

I am pleased that the hosts of this conference are the presidents and chancellors of eight universities, and that the Steering Committee is drawn equally from universities and

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*Presented at the National Conference on University-Corporate Relations in Science and Technology, sponsored by the University of Pennsylvania, Philadelphia, Pennsylvania, December 16, 1982.

**Director, National Institutes of Health, Bethesda, Maryland 20205

INDUSTRY. THE ISSUES AND PROBLEMS BEING ADDRESSED ARE PRIMARILY AT THE INTERFACE BETWEEN ACADEMIA AND THE CORPORATE WORLD. THE COMPOSITION OF THE ORGANIZING AND PLANNING BODIES OF THIS CONFERENCE IS ITSELF A RECOGNITION OF THIS STATEMENT. THERE HAVE BEEN SUGGESTIONS THAT GOVERNMENT, FOR EXAMPLE NIH, SHOULD ORGANIZE SUCH A CONFERENCE. NIH HAS NOT DONE SO. WE BELIEVE IT PREFERABLE THAT THESE NEW RELATIONSHIPS EVOLVE AS THEY HAVE, WITH GOVERNMENT SERVING A FACILITATIVE ROLE. GOVERNMENT SUPPORTS RESEARCH BECAUSE IT IS IN THE NATIONAL INTEREST AND ESSENTIAL TO THE WELFARE AND SECURITY OF THE NATION. IT SUPPORTS BOTH THE ACQUISITION OF NEW KNOWLEDGE AND THE APPLICATION OF SUCH KNOWLEDGE TO THE SOLUTION OF SOCIETAL PROBLEMS. MAINTAINING A HEALTHY ECONOMY IS ALSO AN IMPORTANT GOVERNMENT RESPONSIBILITY. TECHNOLOGY TRANSFER IS AN ENERGETIC EMPHASIS OF GOVERNMENT, TO INSURE THAT THE PUBLIC GOOD IS SERVED BOTH THROUGH THE APPROPRIATE APPLICATION OF RESEARCH RESULTS AND THE DEVELOPMENT OF ECONOMIC WELL-BEING OF THE COUNTRY.

BUT THIS CONFERENCE, AND THE ACTIVITIES OF SEVERAL PREDECESSOR BODIES, SUCH AS THE NATIONAL COMMISSION ON RESEARCH, THE PAJARO DUNES CONFERENCE, AND THE AAU INDUSTRY/UNIVERSITY COMMITTEE, ALL INDICATE A SUBSTANTIAL LEVEL OF CONCERN OVER THE RISK/BENEFIT RATIO OF THESE NEW RELATIONSHIPS, PARTICULARLY TO THE TRADITIONAL BASIC VALUES OF THE UNIVERSITY. WE HAVE HEARD CONCERNS EXPRESSED ABOUT THE PERVASIVE INFLUENCE OF COMMERCIALIZATION ON THE CHOICE OF SCIENTIFIC QUESTIONS

ADDRESSSED BY FACULTY--ON THEIR SELECTION OF RESEARCH IDEAS; IF MARKETABILITY AND THE QUEST FOR FINANCIAL REWARDS DRIVE THEIR DECISIONS; ON OPEN EXCHANGE OF IDEAS; ON PROMPT AND OBJECTIVE PUBLICATION. THESE NEW RELATIONSHIPS ADD A FURTHER TEST OF FACULTY LOYATIES AND COMMITMENTS, SUPERIMPOSED ON THOSE ALREADY GENERATED BY ACADEMIC-GOVERNMENTAL FUNDING REALITIES. AND YESTERDAY WE HEARD THE EXPRESSION OF A FULL GAMUT OF OPINION, RANGING FROM DEEP SKEPTICISM THAT THE UNIVERSITY COULD ACCOMMODATE TO THESE NEW INDUSTRIAL LINKAGES WITHOUT HAVING TO PAY A DISASTEROUS PRICE, TO ASSURANCES THAT IN THE PARTICULARS OF A DEFINED SITUATION THE POTENTIAL FOR ADEQUATE SAFEGUARDS COULD READILY BE DISCERNED. THE COLLOQUY REMINDED ME FURTHER OF A BERMUDA TRIANGLE, AND OF THE NECESSITY FOR CAUTIOUS AND DELIBERATE SAILING.

I AM HERE TODAY AS DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH, THE AGENCY THROUGH WHICH THIS NATION SUPPORTS AND CONDUCTS A BIOMEDICAL RESEARCH ENTERPRISE THAT IS SECOND TO NONE. BECAUSE OF THAT RESPONSIBILITY, NIH HAS AN IMPORTANT STAKE IN THE ISSUES UNDER DISCUSSION. NIH IS OF COURSE UTTERLY DEPENDENT UPON BOTH A FREE UNIVERSITY AND A CREATIVE INDUSTRY FOR THE ACCOMPLISHMENT OF ITS MISSION. ANY ACTIVITY THAT AFFECTS THE PROGRESS OF HEALTH RESEARCH AND THE APPLICATION OF ITS FINDINGS FOR THE BENEFIT OF PEOPLE IS OF CONCERN TO US.

It is the confluence of several forces that brings us together in this and similar conferences: the rapid pace of discovery, the range of implications in today's biomedical science and technology, and the practical applications of new knowledge that are only beginning to be realized. We are overwhelmed by riches and opportunities, just at a time when instability of Federal support of science is sending shock waves of apprehension throughout the academic community. It is no wonder that we must wrestle with questions of management and organization of the research-development-application endeavor. Organizational questions, as well as broader issues such as ethical considerations, would have arisen at this stage even without a downturn in the economic situation, both in general and within the research enterprise.

The period of explosive growth of support for biomedical research of the 50s and 60s, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. After reaching a high in constant dollars in 1979, the NIH budget leveled off, and in the past three years has declined about 12 percent in the same dollars. In the context of the present economy, NIH has been well treated by the Administration and the Congress, but it cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new, steady state that all of us, NIH,

UNIVERSITIES, AND INDUSTRY ALIKE, WOULD DO WELL TO VIEW AS THE FUTURE NORM.

SINCE IT MAY NOT BE POSSIBLE TO CONTINUE AT PRESENT LEVELS ALL OF THE EFFORTS AND PROGRAMS WE HAVE COME SO PASSIONATELY TO CHERISH, WE WILL HAVE TO SET OUR RESEARCH PRIORITIES CAREFULLY, TAKING INTO CONSIDERATION SUCH FACTORS AS THE OVERALL MISSION OF NIH TO SUPPORT RESEARCH IN PURSUIT OF HEALTH, SCIENTIFIC OPPORTUNITY, AND PUBLIC MANDATES AND ASSIGNMENTS EXPRESSED BY CONGRESS AND THE ADMINISTRATION. NEVERTHELESS, THERE ARE CERTAIN ABIDING PRINCIPLES THAT WILL CONTINUE TO GUIDE OUR DECISIONS.

ONE IS THAT THE PURSUIT OF BASIC KNOWLEDGE IS THE FOUNDATION OF ALL PROGRESS IN THE HEALTH SCIENCES. WE MUST CONTINUE TO INCREASE OUR STORE OF FUNDAMENTAL KNOWLEDGE. ANY RELAXATION OF THAT NECESSARILY LONG-TERM OBJECTIVE IN FAVOR OF SHORT-TERM ADVANTAGE IS A THREAT TO THE EVENTUAL TRIUMPH OVER DISEASE AND SUFFERING.

A SECOND FUNDAMENTAL PRINCIPLE IS THAT INVESTIGATOR-INITIATED RESEARCH INTO BIOLOGICAL PROCESSES HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY. THROUGH COMPETING RESEARCH PROJECTS, WE TAP THE BEST MINDS AND MOST CREATIVE IDEAS, WEIGH THEM THROUGH PEER REVIEW OF SUBSTANCE AND METHODOLOGY, AND TEST AND REFINE THEM THROUGH CHALLENGE AND OPEN EXCHANGE OF INFORMATION. NIH WILL CONTINUE TO PLACE TOP PRIORITY ON NEW AND

COMPETING RESEARCH PROJECT GRANTS, AND ON THE SUPPORT OF SUCH PROJECTS FOR THE LIFE OF THE AWARD PERIOD. IN THE PAST SEVERAL YEARS, NIH HAS SHIFTED RESOURCES FROM ALMOST ALL OTHER MECHANISMS IN ORDER TO FUND A STABLE NUMBER OF NEW AND COMPETITIVE RENEWAL AWARDS. IN FY 1982, JUST ENDED, WE FUNDED 5,030 SUCH AWARDS, ALMOST 300 MORE THAN INITIALLY ANTICIPATED.

FINALLY, THE THIRD ELEMENT OF THESE TIMELESS PRINCIPLES IS THAT IT IS ESSENTIAL TO ASSURE A CONTINUING SUPPLY OF WELL-TRAINED SCIENTISTS TO CONDUCT RESEARCH IN THE FUTURE. THERE IS A CLOSE INTERRELATIONSHIP BETWEEN PRODUCTIVITY IN RESEARCH AND THE AVAILABILITY AND REPLENISHMENT OF THE SUPPLY OF QUALIFIED INVESTIGATORS.

WITH THESE PRINCIPLES AS A FOUNDATION, OUR PRIMARY PRIORITY AT NIH WILL CONTINUE TO BE SUPPORT OF BASIC BIOMEDICAL RESEARCH WHICH IS CONDUCTED MAINLY IN UNIVERSITY LABORATORIES. THE BULK OF SUPPORT FOR THAT PURPOSE WILL CONTINUE TO COME FROM THE FEDERAL GOVERNMENT, PRIMARILY THROUGH NIH.

IN 1981, FOR EXAMPLE, AN ESTIMATED 78 PERCENT OF HEALTH R&D FUNDS USED BY UNIVERSITIES CAME FROM THE FEDERAL GOVERNMENT; 19 PERCENT FROM UNIVERSITY, STATE, LOCAL AND OTHER NON-PROFIT SOURCES; AND THREE PERCENT FROM INDUSTRY. WHILE INDUSTRY HAS AN IMPORTANT ROLE IN THE CONTINUUM OF HEALTH SCIENCE RESEARCH, ITS EMPHASIS IS CHIEFLY ON DEVELOPMENT AND APPLICATION. DURING MOST

OF THE HISTORY OF NIH, CERTAINLY FOR THE PAST TEN TO 15 YEARS, ABOUT FOUR-FIFTHS OF THE AGENCY'S BUDGET HAS BEEN EXPENDED IN GRANTS AND CONTRACTS AWARDED TO OTHER INSTITUTIONS FOR THE SUPPORT OF RESEARCH. I SHOULD MENTION THAT, WHILE THE NIH CAMPUS IN BETHESDA IS THE LARGEST SINGLE BIOMEDICAL RESEARCH INSTITUTION IN THE WORLD, IT ACCOUNTS FOR ONLY ABOUT FOUR OUT OF EVERY 100 DOLLARS SPENT ON SUCH WORK IN THE UNITED STATES.

I MENTIONED EARLIER THAT IN MY JUDGMENT THE BUDGET FOR BIOMEDICAL RESEARCH, MORE SPECIFICALLY THE BUDGET OF NIH, COULD NOT BE EXPECTED TO GROW SUBSTANTIALLY IN CONSTANT DOLLARS IN THE IMMEDIATE FUTURE. BUT IT IS A VERY LARGE BUDGET, ABOUT $3.6 BILLION IN FY 1982, TENDING TOWARD $3.9 BILLION OR EVEN $4.0 BILLION IN FY 1983.

I BRING UP THESE PRINCIPLES, PRIORITIES AND FISCAL MATTERS TO CONFIRM PROJECTIONS MADE AT THIS CONFERENCE AND ELSEWHERE: FEDERAL FUNDING FOR BIOMEDICAL RESEARCH WILL BE IN A STEADY STATE FOR THE FORESEEABLE FUTURE. UNIVERSITIES ARE IN NEED OF FINANCIAL SUPPORT AND IT IS TO BE EXPECTED THAT EFFORTS TO FIND NEW KINDS OF ARRANGEMENTS WITH INDUSTRY WILL INTENSIFY IN THE FUTURE. INDUSTRY NEEDS THE IDEAS AND TRAINED SCIENTISTS PRODUCED BY ACADEMIA, WITH FEDERAL SUPPORT. AND, FROM THE GOVERNMENT, OR NIH, POINT OF VIEW, WE NEED THE COOPERATIVE EFFORTS OF INDUSTRY AND ACADEMIA IN ORDER TO CARRY OUT OUR MISSION TO CONDUCT AND SUPPORT RESEARCH FOR THE PUBLIC GOOD. IF THERE IS A REDUCTION IN

THE FLOW OF IDEAS AND TRAINED SCIENTISTS, OR AN INTERRUPTION IN THE TIMELY APPLICATION OF KNOWLEDGE IN PRACTICE, OUR OBJECTIVE CANNOT BE FULLY REALIZED. IT IS IN THE INTEREST OF ALL THREE PARTNERS IN THE TRIANGLE TO MAKE MAXIMUM USE OF RESOURCES AND ABILITIES AND TO DEVELOP THE ORGANIZATIONAL ARRANGEMENTS THAT WILL MAKE THIS POSSIBLE. OUR PAST RECORD OF ACHIEVEMENT THROUGH COLLABORATION AND COOPERATION IS A SOLID BASIS ON WHICH TO BUILD.

THE COMBINING OF FORCES TO SOLVE PROBLEMS AND TO MAKE MAXIMUM USE OF OUR RESOURCES HAS A VERY LONG HISTORY IN THE UNITED STATES. ONE CAN GO BACK TO THE MORRILL ACT OF 1862 WHICH PROVIDED MASSIVE FEDERAL SUPPORT TO HIGHER EDUCATION AND GAVE IMPETUS TO SCIENTIFIC FARMING TO CREATE THE AGRICULTURAL INDUSTRY THAT TODAY FEEDS THE NATION AND A GOOD PART OF THE WORLD. ONE RECALLS THE 1950S WHEN FEDERAL SUPPORT FOR EDUCATION AND RESEARCH LED TO GREAT ADVANCES IN THE PHYSICAL AND ENGINEERING SCIENCES. COLLABORATION AMONG GOVERNMENT, ACADEMIA AND INDUSTRY CARRIED US TO THE MOON AND BEYOND AND LED TO KNOWLEDGE AND TECHNOLOGY FROM WHICH WE ARE STILL REAPING HUGE SOCIAL AND ECONOMIC BENEFITS. FEARS OF NEGATIVE IMPACT ON THE FREEDOM AND INTEGRITY OF HIGHER EDUCATION WERE VOICED THEN. COOPERATION IN RESEARCH <u>AND</u> IN ORGANIZATIONAL PROBLEM-SOLVING OVERCAME OBSTACLES AND BROUGHT US SUCCESSFULLY INTO A NEW ERA OF ACHIEVEMENT.

THE FEDERAL INVESTMENT EXTENDED TO THE HEALTH SCIENCES. RAPID EXPANSION OF NIH SUPPORT FOR BIOMEDICAL RESEARCH PLAYED A

MAJOR ROLE IN THE TRANSFORMATION OF MEDICAL SCIENCE. INDUSTRY HAS BEEN HEAVILY INVOLVED IN THE DEVELOPMENT AND APPLICATION OF HEALTH RESEARCH FINDINGS FROM THE BEGINNING.

LET ME CITE JUST A FEW STATISTICS THAT INDICATE THE SCOPE OF COLLABORATION IN HEALTH RESEARCH AND DEVELOPMENT AMONG GOVERNMENT, ACADEMIA, AND INDUSTRY--AND THE DIFFERENT "ASSIGNMENTS" WE EACH PERFORM WITHIN THAT COLLABORATION. REMEMBER THAT 60 PERCENT OF ALL RESEARCH FUNDED BY NIH IS PERFORMED BY UNIVERSITIES.

TOTAL NATIONAL SUPPORT FOR HEALTH R&D IN 1981 WAS AN ESTIMATED $8.6 BILLION. OF THAT TOTAL, 39 PERCENT WAS SUPPORTED BY NIH, 33 PERCENT BY INDUSTRY, AND 28 PERCENT BY OTHER FEDERAL, STATE AND LOCAL GOVERNMENTS AND PRIVATE NON-PROFIT ORGANIZATIONS. BUT WHEN WE LOOK AT ALL BASIC HEALTH RESEARCH SUPPORT, WHICH TOTALED SOME $2.8 BILLION, 63 PERCENT WAS PROVIDED BY NIH AND ABOUT 10 PERCENT BY INDUSTRY.

BREAKING DOWN THOSE FIGURES FURTHER, BY TYPE OF EFFORT SUPPORTED, WE FIND THESE COMPARISONS: NIH SUPPORT IN 1981 WAS ALLOCATED APPROXIMATELY 53 PERCENT TO BASIC RESEARCH, 35 PERCENT TO APPLIED RESEARCH AND 12 PERCENT TO DEVELOPMENT. OUR INTERNAL ANALYSIS OF STATISTICS FROM VARIOUS SOURCES FOUND A DIFFERENT, BUT ANTICIPATED, TREND IN INDUSTRY SUPPORT: 10 PERCENT FOR BASIC

RESEARCH, 45 PERCENT FOR APPLICATION, AND 45 PERCENT FOR DEVELOPMENT.

IT IS CLEAR, THEN, THAT GOVERNMENT AND ACADEMIA AND INDUSTRY PERFORM COMPLEMENTARY ROLES IN THE ADVANCEMENT AND APPLICATION OF BIOMEDICAL KNOWLEDGE. ONE FREQUENTLY DESCRIBES THIS SYSTEM OF SHARED RESPONSIBILITIES AS A "CONTINUUM" FROM BASIC RESEARCH FINDINGS TO APPLICATION IN MEDICAL PRACTICE. A MORE APPROPRIATE DESCRIPTION WOULD BE A VENN DIAGRAM WITH ITS INTERSECTING CIRCLES, OR A RUBIK'S CUBE WITH ITS MULTI-FACETED ALIGNMENTS.

I MIGHT MENTION, INCIDENTALLY, THAT INDUSTRY HAS CAPITALIZED ON SOME FINDINGS OF BIOMEDICAL RESEARCH IN AREAS UNRELATED TO HEALTH. A REVIEW BY THE NIH OFFICE FOR MEDICAL APPLICATIONS OF RESEARCH FOUND TEN BIOMEDICAL DISCOVERIES ADOPTED BY INDUSTRY FOR PURPOSES OTHER THAN HEALTH SERVICES. THEY INCLUDE, FOR EXAMPLE:

- o FREEZE-DRYING, FIRST DEVELOPED IN BIOMEDICAL LABORATORIES FOR PRESERVING PROTEINS WITHOUT REFRIGERATION; ITS USE IN THE FOOD INDUSTRY IS FAMILIAR TO YOU, I AM SURE.

- o THE LABORATORY INSTRUMENT COMPUTER, CALLED LINC, WAS THE FIRST DESK MONITOR THAT COULD PERFORM BIOMEDICAL COMPUTATIONS AND INTERACT WITH EXPERIMENTAL EQUIPMENT IN THE LABORATORY; THIS DISCOVERY CONTRIBUTED TO MINICOMPUTER DEVELOPMENT.

- o Enzyme biochemistry, a field that has received significant contributions from biomedicine, has been applied in the production of (among other things) beer, leather products and laundry detergents.

These examples, plus seven others in the survey, were conservatively estimated to contribute some $37 billion annually to the Gross National Product, a figure that exceeds the total of combined appropriations for NIH since 1937; and is ten times greater than the NIH budget for fiscal year 1982.

The point I seek to emphasize today is that the current rise of special arrangements between industry and academia designed to advance research and development in health science is not a radical departure from tradition. These arrangements can be fairly described as variations, or modifications, within existing umbrella relationships created to take advantage of scientific and technological developments of recent years, not unlike those well-established in engineering, chemistry, and physics. The "suddenness" of their appearance on the biomedical scene arises from the rapidity of recent scientific discoveries with practical implications.

I tend to agree with the general viewpoint on this subject expressed recently by the American Association of Universities in response to a request by Congressmen Gore and Fuqua. This view

IS THAT THE "ACADEMIC WORLD IS REASONABLY WELL IN COMMAND OF AN IMPORTANT SET OF ISSUES" AND THAT GOOD FAITH EFFORTS, BASED UPON PAST EXPERIENCE, CAN BE EXPECTED TO RESOLVE PROBLEMS RAISED BY CURRENT UNIVERSITY-INDUSTRY RESEARCH AND DEVELOPMENT ARRANGEMENTS.

THE GOVERNMENT, OR NIH, POSITION IN REGARD TO CORPORATE-UNIVERSITY RELATIONSHIPS RANGES FROM NARROW, TECHNICAL RESPONSIBILITIES TO BROAD MANDATES. NIH HAS STATUTORY RESPONSIBILITIES IN SUCH AREAS AS THE AWARD OF GRANTS AND CONTRACTS AND THEIR PROPER PERFORMANCE UNDER FISCAL REQUIREMENTS AND GUIDELINES CONCERNING SUCH MATTERS AS MISCONDUCT IN RESEARCH AND RECOMBINANT DNA EXPERIMENTATION. WE ALSO HAVE SPECIFIC RESPONSIBILITIES UNDER THE PATENT AND TRADEMARK AMENDMENTS OF 1980. UNDER REQUIREMENTS OF LAW AND REGULATION, NIH COULD TAKE AN ARMS-LENGTH STANCE IN REGARD TO CORPORATE-UNIVERSITY CONTRACTS, MAKING CERTAIN ONLY THAT STATUTORY PROVISIONS ARE TECHNICALLY SATISFIED.

BUT, OF COURSE, SPECIFIC RESPONSIBILITIES HAVE BROAD IMPLICATIONS. THE FUNDAMENTAL MISSION OF NIH, AS STATED IN VARIOUS LAWS AND AS DEVELOPED DURING NEARLY A CENTURY, AMOUNTS TO A SOCIAL CONTRACT TO FOSTER THE ADVANCE OF BIOMEDICAL RESEARCH FOR THE PUBLIC BENEFIT. IT IS OUR RESPONSIBILITY IN THIS AREA TO REPRESENT AND PROTECT THE PUBLIC INTEREST AND, THEREFORE,

ARRANGEMENTS THAT INVOLVE FEDERAL INVESTMENT ARE OF CONCERN TO US.

ONE EXAMPLE OF THE WAY IN WHICH NIH CAN BE HELPFUL IN SUCH ARRANGEMENTS IS OUR EXPERIENCE WITH THE AGREEMENT BETWEEN MASSACHUSETTS GENERAL HOSPITAL (MGH) AND HOECHST AG. AT THE INVITATION OF MGH, STAFF MEMBERS FROM THE DEPARTMENT OF HEALTH AND HUMAN SERVICES MET WITH REPRESENTATIVES OF THE HOSPITAL TO ASSESS THE CONTRACT AND CLARIFY QUESTIONS RAISED BY EITHER GROUP. WE UNDERSCORED THE APPLICABILITY OF THE PATENT LAW AND REGULATIONS TO ANY INVENTIONS OR PRODUCTS ARISING FROM THAT ENDEAVOR, TO THE EXTENT THAT FEDERAL FUNDS CONTRIBUTED DIRECTLY. MGH OFFICIALS DEMONSTRATED THAT THEY UNDERSTOOD THEIR RESPONSIBILITIES AND ASSURED US THAT THEY INTENDED TO COMPLY FULLY WITH THE LAW AND REGULATIONS. WE WERE SATISFIED THAT THE GOVERNMENT'S RIGHTS CAN BE PROTECTED ADEQUATELY UNDER TERMS OF THE MGH-HOECHST AGREEMENT. WE ARE PREPARED TO ENGAGE IN SIMILAR DISCUSSIONS WITH OTHER NIH GRANTEES OR CONTRACTORS WHO HAVE MADE, OR ARE CONTEMPLATING, SIMILAR ARRANGEMENTS WITH PRIVATE INDUSTRY. WE BELIEVE THAT SUCH INFORMATION EXCHANGE WELL IN ADVANCE OF ANY INVENTIONS UNDER THESE JOINT VENTURES WILL DO MUCH TO PREVENT DISCORD OR OTHER DIFFICULTIES WHEN RESULTS OF POTENTIAL COMMERCIAL INTEREST BEGIN TO EMERGE.

WE DO NOT FORESEE A REGULATORY ROLE OR DIRECT PARTICIPATION OF NIH IN SUCH CORPORATE-UNIVERSITY ARRANGEMENTS. BUT WE DO SEE

THE AGENCY AS A PARTY OF INTEREST, INSOFAR AS SUCH CONTRACTS AFFECT OUR BASIC MISSION AND STATUTORY REQUIREMENTS. THERE ARE TWO GENERAL WAYS IN WHICH NIH CAN CONTRIBUTE TO THE DEVELOPMENT OF NEW WORKING ARRANGEMENTS BETWEEN INDUSTRY AND ACADEMIA AND TO CONTINUED STRENGTHENING OF THE GOVERNMENT-UNIVERSITY-INDUSTRY PARTNERSHIP. ONE IS TO PROVIDE ADVICE AND TECHNICAL ASSISTANCE TO THE PARTIES IN SUCH CONTRACTS, AS REQUESTED. THE OTHER IS TO ENHANCE THE CLIMATE OF COLLABORATION THAT WILL ASSURE CONTINUED GROWTH OF THE BIOMEDICAL KNOWLEDGE BASE AND ITS APPLICATION TO PUBLIC HEALTH BENEFITS. WE ARE CONTRIBUTING TO THE LATTER IN SEVERAL WAYS.

NIH TAKES AN ACTIVE ROLE IN TECHNOLOGY TRANSFER, FOR EXAMPLE. IN 1977, NIH ESTABLISHED THE OFFICE FOR MEDICAL APPLICATIONS OF RESEARCH WHICH IS THE FOCAL POINT FOR OUR EFFORTS TO TRANSLATE THE RESULTS OF BIOMEDICAL RESEARCH INTO THE PRACTICE OF MEDICINE. ONE OF ITS MAIN FUNCTIONS IS TO COORDINATE CONSENSUS DEVELOPMENT CONFERENCES ON SPECIFIC TOPICS IN MEDICINE. IN THIS PROCESS BIOMEDICAL INVESTIGATORS, HEALTH PROFESSIONALS AND OTHERS, INCLUDING REPRESENTATIVES OF INDUSTRY, ARE BROUGHT TOGETHER TO ASSESS DATA ON A SPECIFIC HEALTH CARE TECHNOLOGY. AND, OF COURSE, THE NATIONAL LIBRARY OF MEDICINE IS ENGAGED IN TIMELY DISSEMINATION OF THE KNOWLEDGE SECURED BY OUR RESEARCH ARMS. THE LIBRARY IS MORE THAN A STOREHOUSE OF BIOMEDICAL INFORMATION; IT IS THE HEART OF A NATIONAL AND WORLDWIDE NETWORK THAT OFFERS TO SCIENTISTS, MEDICAL

PRACTITIONERS AND OTHERS THE INFORMATION NEEDED TO CONDUCT RESEARCH, AND APPLY ITS FINDINGS.

ANOTHER IMPORTANT ELEMENT OF TECHNOLOGY TRANSFER IS CLINICAL TRIALS. NIH HAS SPONSORED SEVERAL LARGE CLINICAL TRIALS TO IMPROVE THE PREVENTION AND TREATMENT OF CORONARY HEART DISEASE, HYPERTENSION, AND DIABETES. AS YOU KNOW, CLINICAL TRIALS OF NEW DRUGS, DEVICES AND TECHNIQUES ARE ESSENTIAL, COSTLY AND TIME CONSUMING. A MAJOR RESPONSIBILITY FOR SUCH TRIALS RESTS WITH THE GOVERNMENT, BUT IS IS AN ACTIVITY IN WHICH THERE IS ROOM FOR GREATER PARTICIPATION BY INDUSTRY.

ANOTHER AREA IN WHICH A MAJOR AND CONTINUING ROLE MUST BE PLAYED BY THE GOVERNMENT IS IN ORPHAN DRUG AND DEVICE TESTING AND DEVELOPMENT. IN THIS CONNECTION, I WANT TO MENTION THE ORPHAN PRODUCTS BOARD ESTABLISHED BY THE DEPARTMENT. NIH, AND OTHER DEPARTMENTAL AGENCIES, ARE REPRESENTED ON THE BOARD WHICH, AMONG OTHER THINGS, IDENTIFIES ORPHAN PRODUCTS THAT NEED DEVELOPMENT OR OTHER ASSISTANCE IN ORDER TO SECURE MARKETING APPROVAL. AS PART OF ITS EFFORT TO STIMULATE ORPHAN PRODUCT RESEARCH, DEVELOPMENT AND MARKETING, THE BOARD WILL ENCOURAGE PRIVATE INITIATIVES AND GOVERNMENT EFFORT WHERE APPROPRIATE.

THESE AREAS OF ACTIVITY--TECHNOLOGY TRANSFER, CLINICAL TRIALS, AND DRUG AND DEVICE DEVELOPMENT--ARE DIRECT RESPONSIBILITIES OF THE GOVERNMENT IN WHICH BOTH UNIVERSITIES AND

INDUSTRY ARE HEAVILY INVOLVED. THERE ARE OTHER WAYS IN WHICH WE PROMOTE THE COMMERCIALIZATION OF RESEARCH TO CONVEY SCIENTIFIC FINDINGS INTO MEDICAL PRACTICE.

HISTORICALLY, THE DEPARTMENT, AND PARTICULARLY NIH, HAVE HAD IN PLACE PATENT POLICIES THAT ALLOW UNIVERSITIES AND OTHER NON-PROFIT ORGANIZATIONS TO OWN THE INVENTIONS DEVELOPED WITH NIH FUNDS. THIS HAS FACILIATED THEIR ABILITY TO PATENT THEIR INVENTIONS AND BRINGING THEM TO COMMERCIAL APPLICATION. FOR EXAMPLE, DURING THE PAST 15 TO 20 YEARS, SOME 1,000 PATENTS HAVE BEEN OBTAINED ON NIH-SUPPORTED WORK, 49 PERCENT OF WHICH HAVE BEEN LICENSED. IT HAS BEEN REPORTED TO US BY OUR GRANTEES THAT CAPITAL INVESTED TO COMMERCIALIZE THESE PATENTS IS APPROXIMATELY $35 MILLION AND THAT GROSS SALES OF THE PRODUCTS AMOUNTS TO $190 MILLION. THE PATENT AND TRADEMARK AMENDMENT ACT OF 1980, IN EFFECT, CODIFIED IN LAW THE DEPARTMENTAL AND NIH PATENT POLICY. IT IS TOO EARLY TO FORESEE THE IMPACT OF THE LAW, BUT WE EXPECT THAT COMMERCIALIZATION OF NIH-SUPPORTED INVENTIONS WILL REMAIN AT ITS HISTORICALLY HIGH RATE OR, EVEN, INCREASE.

WE ARE REACHING OUT TO INDUSTRY UNDER A DEPARTMENTAL ACTION WHICH, LAST JANUARY, MADE FOR-PROFIT ORGANIZATIONS ELIGIBLE FOR GRANTS FROM THE DEPARTMENT AND NIH. WE ARE ADVERTISING THAT FACT AND ARE REQUESTING NOMINATIONS OF ADDITIONAL SCIENTISTS FROM THE FOR-PROFIT SECTOR TO SERVE ON OUR PEER REVIEW GROUPS. ALTHOUGH PRIVATE SECTOR SCIENTISTS HAVE PARTICIPATED IN THESE COMMITTEES

FOR SEVERAL YEARS, WE BELIEVE THAT WE SHOULD ENLARGE THE NUMBER OF REVIEWERS WHO HAVE HAD FIRST-HAND EXPERIENCE IN SUCH SETTINGS. FOR-PROFIT FIRMS HAVE, OF COURSE, LONG BEEN ELIGIBLE FOR CONTRACTS WITH NIH.

ANOTHER INDUSTRY-ORIENTED INITIATIVE OF NIH IS UNDER THE SMALL BUSINESS INNOVATION DEVELOPMENT ACT OF 1982. UNDER THAT LAW, FEDERAL AGENCIES, INCLUDING NIH, WITH ANNUAL R&D BUDGETS EXCEEDING $100 MILLION ARE REQUIRED TO SET ASIDE A CERTAIN AMOUNT OF THEIR EXTRAMURAL R&D BUDGETS ANNUALLY FOR A SMALL BUSINESS INNOVATION RESEARCH PROGRAM. THE ACT IS DESIGNED TO: STIMULATE TECHNOLOGICAL INNOVATION; USE SMALL BUSINESS TO MEET FEDERAL RESEARCH AND DEVELOPMENT NEEDS; INCREASE PRIVATE SECTOR COMMERCIALIZATION OF INNOVATIONS DERIVED FROM FEDERAL RESEARCH AND DEVELOPMENT; AND TO FOSTER AND ENCOURAGE PARTICIPATION BY MINORITY AND DISADVANTAGED PERSONS IN TECHNOLOGICAL INNOVATION.

WE ARE INTENSIFYING OUR EFFORTS TO IDENTIFY SMALL R&D FIRMS WITH EXPERTISE AND INTERESTS IN BIOMEDICAL SCIENCE AND ARE ASKING THEM TO PROVIDE RESUMES OF CAPABILITIES. THE PUBLIC HEALTH SERVICE HAS ISSUED AN OPEN INVITATION TO SMALL BUSINESS R&D FIRMS TO PARTICIPATE IN A CONFERENCE ON THIS PROGRAM AT NIH NEXT FEBRUARY. A SOLICITATION FOR GRANT APPLICATIONS WILL BE AVAILABLE SOON WITH DETAILED INFORMATION ON THE PROGRAM, GRANT APPLICATION AND REVIEW PROCEDURES AND R&D NEEDS WHICH LEND THEMSELVES TO PERFORMANCE BY SMALL BUSINESS.

THE AREA OF BASIC RESEARCH THAT MORE THAN ANY OTHER ACCOUNTS FOR OUR BEING HERE TODAY IS WHAT WE BROADLY TERM "GENETIC MANIPULATION." NIH FUNDING FOR PROJECTS IN THIS AREA INCREASED FROM $61 MILLION FOR 554 PROJECTS IN 1978 TO $184 MILLION FOR 1,523 PROJECTS IN FISCAL YEAR 1982 (NEARLY 10 PERCENT OF OUR EXTRAMURAL RESEARCH PORTFOLIO). WE EXPECT THAT USE OF RECOMBINANT DNA TECHNIQUES IN RESEARCH WILL CONTINUE TO INCREASE. A SECOND AREA IS NOT FAR BEHIND. AN INDICATION OF THE WIDESPREAD USE OF MONCLONAL ANTIBODIES, HYBRIDOMAS AND CELL FUSION TECHNOLOGY CAN BE SEEN FROM FISCAL YEAR 1980 FIGURES, THE LATEST COMPLETE SET IN HAND. A TOTAL OF 553 AWARDS FOR FUNDING OF $48 MILLION WERE MADE DURING FISCAL 1980. IN ADDITION, THESE TECHNOLOGIES WERE USED IN 90 INTRAMURAL PROJECTS SUPPORTED BY SEVEN OF OUR BUREAUS, INSTITUTES AND DIVISIONS.

OF SPECIAL INTEREST TO OUR INDUSTRIAL PARTNERS ARE TWO RESEARCH SUPPORT SERVICES NOW AVAILABLE. ONE IS ESTABLISHMENT, UNDER CONTRACT, OF THE HUMAN GENETIC MUTANT CELL REPOSITORY AT THE INSTITUTE FOR MEDICAL RESEARCH IN CAMDEN, NEW JERSEY. THIS CELL BANK WAS CREATED TO STIMULATE AND FACILITATE RESEARCH ON HUMAN GENETIC DISORDERS. IT PROVIDES INVESTIGATORS WITH CELL LINES FROM PATIENTS WITH COMMON OR RARE HEREDITARY DISEASES. THE CELL LINES ARE BEING WIDELY DISTRIBUTED: 3,972 CULTURES WERE DISTRIBUTED IN 1981. AND, EFFECTIVE JUST TWO MONTHS AGO, IS THE ON-LINE AVAILABILITY OF THE GENETIC SEQUENCE DATA BANK, CALLED GENBANK, IN CAMBRIDGE, MASSACHUSETTS. IT WILL BE A REPOSITORY

FOR ALL PUBLISHED NUCLEIC ACID SEQUENCES GREATER THAN 50 BASE PAIRS IN LENGTH, CATALOGUED AND ANNOTATED FOR SITES OF BIOLOGICAL INTEREST.

THESE, THEN, ARE SOME OF THE WAYS IN WHICH NIH IS WORKING TO ENCOURAGE TECHNOLOGY TRANSFER. THERE ARE TWO AREAS IN PARTICULAR IN WHICH THE PRIVATE SECTOR COULD EXPAND ITS ACTIVITY AND, THEREBY, RELIEVE SOME OF THE FINANCIAL PRESSURE ON ITS ACADEMIC AND GOVERNMENT PARTNERS. THESE ARE TRAINING OF SCIENTIFIC INVESTIGATORS AND THE CONDUCT OF CLINICAL TRIALS--ACTIVITIES THAT WILL BRING RETURNS TO INDUSTRY, TO THE RESEARCH ENTERPRISE AND, UTIMATELY, TO THE GENERAL PUBLIC.

THE IMPORTANCE OF TRAINING AND THE DEVELOPMENT OF A CADRE OF ABLE IVESTIGATORS TO ACADEMIA AND INDUSTRY AND FUTURE BIOMEDICAL ADVANCES IS OBVIOUS. THE SUPPORT OF TRAINING IS AMONG THE HIGHEST PRIORITIES OF NIH. INDUSTRY COULD CONTRIBUTE TO CONTINUITY AND EXPANSION OF THE INVESTIGATOR POOL BY DIRECT SUPPORT OF TRAINING IN ACADEMIC INSTITUTIONS AND BY EXCHANGE ARRANGEMENTS INVOLVING STUDENTS AND ESTABLISHED SCIENTISTS IN UNIVERSITY AND INDUSTRIAL LABORATORIES, FOR EXAMPLE.

BECAUSE OF COMMON INTERESTS, INCREASED PARTICIPATION WITH ACADEMIA AND GOVERNMENT IN CLINICAL TRIALS SHOULD BE ATTRACTIVE TO INDUSTRY. ONE THINKS FIRST OF THE PHARMACEUTICAL AND OTHER MEDICAL PRODUCTS INDUSTRIES IN THIS CONNECTION. THEY HAVE, OF

COURSE, BEEN PARTICIPANTS IN TRIALS WITH SEVERAL OF OUR INSTITUTES. BUT I THINK FURTHER OUTREACH IS IN ORDER--TO THE INSURANCE INDUSTRY, FOR ONE OBVIOUS EXAMPLE. THE NATION'S INSURORS HAVE DEMONSTRATED A STRONG INTEREST IN PROMOTION OF DISEASE PREVENTION AND THE "WELLNESS" CONCEPT. I SUGGEST THAT A SIMILAR SELF-INTEREST MOTIVATION EXISTS FOR PARTICIPATION BY THE INSURANCE INDUSTRY IN CLINICAL TRIALS WHICH ARE DESIGNED TO HAVE A DIRECT EFFECT ON HEALTH.

IN AN ERA OF SUCH GREAT SCIENTIFIC OPPORTUNITY, THERE IS MORE THAN ENOUGH ROOM FOR ALL THREE MEMBERS OF THE GOVERNMENT-INDUSTRY-ACADEMIC TRIANGLE TO ENGAGE THEIR FULL ENERGIES AND RESOURCES. THIS MAXIMUM EFFORT TO TAKE ADVANTAGE OF THE KNOWLEDGE BASE FOR PUBLIC BENEFIT HAS LED TO NEW ARRANGEMENTS AND ALIGNMENTS. WE CAN EXPECT MORE OF THE SAME IN THE FUTURE. WHILE IT IS THE BETTER PART OF WISDOM TO ANTICIPATE THE PROBLEMS THAT ARE LIKELY TO ARISE, WE MUST NOT ALLOW THOSE CONCERNS TO INTERRUPT OUR PROGRESS. WORKING TOGETHER WITH SHARED OBJECTIVES, MEMBERS OF THE GOVERNMENT-INDUSTRY-ACADEMIC HEALTH SCIENCE ENTERPRISE CAN SAFELY NEGOTIATE THE MYTHICAL BERMUDA TRIANGLE AND COME THROUGH HEALTHIER FOR HAVING MADE THE PASSAGE.

REMARKS*

Swearing-In Ceremony

Dr. Harald Löe, Director

National Institute of Dental Research

January 10, 1983

WHEN I BECAME DIRECTOR OF THE NIH LAST SPRING, I WAS AWARE THAT ONE OF MY MOST IMMEDIATE AND POSSIBLY MOST DIFFICULT RESPONSIBILITIES WOULD BE TO FIND THE RIGHT PERSONS FOR SEVERAL MAJOR LEADERSHIP POSITIONS THEN VACANT. ONE SUCH VACANCY WAS THE DIRECTORSHIP OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH.

SO IT WAS WITH PRIDE AND SATISFACTION THAT I WAS ABLE TO ANNOUNCE LAST SEPTEMBER THAT DR. LÖE WOULD BE JOINING US AT THE FIRST OF THE NEW YEAR AS NIDR's DIRECTOR.

TODAY I AM DELIGHTED TO OFFICIALLY PLACE THIS SUCCESSFUL PROGRAM IN HIS CAPABLE HANDS.

AS THE FIFTH DIRECTOR OF NIDR, DR. LÖE WILL PRESIDE OVER ONE OF THE SENIOR COMPONENTS OF THE NATIONAL INSTITUTES OF HEALTH. NIDR WAS THE THIRD INSTITUTE TO BE ESTABLISHED, HAVING BEEN AUTHORIZED IN 1948 ONLY

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*Dr. James B. Wyngaarden, Director,
National Institutes of Health

EIGHT DAYS AFTER THE NATIONAL HEART INSTITUTE WAS CREATED, AND THE NATIONAL INSTITUTE OF HEALTH BECAME OFFICIALLY A PLURAL NAME--THE NATIONAL INSTITUTES OF HEALTH.

THE SAME UNDERSTANDING OF THE POTENTIAL BENEFITS OF DENTAL RESEARCH THAT PROMPTED THE CONGRESS TO FORM NIDR HAS PERSISTED THROUGH THE ENSUING YEARS. THE EARLY CONFIDENCE OF THE CONGRESS HAS BEEN MORE THAN VINDICATED AS THE INSTITUTE HAS GROWN. THE PROGRESSION OF KNOWLEDGE FROM THE FUNDAMENTAL END OF THE RESEARCH CONTINUUM TO ACTUAL APPLICATION IN DENTAL PRACTICE HAS HAD A TREMENDOUS IMPACT ON THE IMPROVEMENT OF THE DENTAL HEALTH OF THE PEOPLE OF OUR NATION.

PREVENTIVE EFFORTS BASED ON INCREASED KNOWLEDGE HAVE BEEN RESPONSIBLE FOR MARKED REDUCTIONS IN THE COST BURDEN OF DENTAL PROBLEMS. HOWEVER, THE CURRENT NATIONAL DENTAL BILL OF $17 BILLION CHALLENGES THE RESEARCH AND PRACTICING COMMUNITY TO MAINTAIN THE MOMENTUM THAT HAS BEEN GENERATED FOR THE PREVENTION OF ALL DENTAL DISEASES AND DISORDERS.

THE ACCOMPLISHMENTS OF THE PAST THIRTY-FOUR YEARS HAVE BEEN THE PRODUCT OF JOINT EFFORTS. THE NIDR HAS BEEN A PARTNER IN THESE SUCCESSFUL ACTIVITIES WITH

PROFESSIONAL GROUPS, PARTICULARLY THE AMERICAN DENTAL ASSOCIATION, THE INTERNATIONAL ASSOCIATION FOR DENTAL RESEARCH, THE AMERICAN ASSOCIATION FOR DENTAL RESEARCH, AND THE AMERICAN ASSOCIATION OF DENTAL SCHOOLS. THE SUPPORT OF THESE GROUPS HAS BEEN CONSTANT AND ALWAYS CONSTRUCTIVE. WE ARE GRATEFUL FOR THE PRESENCE HERE TODAY OF THEIR REPRESENTATIVES.

THE NIDR HAS ALSO BEEN AN EFFECTIVE PARTNER WITH ALL COMPONENTS OF THE NATIONAL INSTITUTES OF HEALTH AND WITH OTHER FEDERAL RESEARCH ACTIVITIES, SUCH AS THE NATIONAL BUREAU OF STANDARDS, THE ARMED FORCES INSTITUTE OF PATHOLOGY, THE NATIONAL NAVAL MEDICAL CENTER, THE WALTER REED ARMY MEDICAL CENTER AND OTHERS IN PROGRAMS OF FUNDAMENTAL RESEARCH. SCIENTISTS OF NIDR HAVE MADE NOTABLE CONTRIBUTIONS ACROSS A WIDE SPECTRUM, INCLUDING HIGHLY PRODUCTIVE STUDIES IN BIOCHEMISTRY, IMMUNOLOGY, MICROBIOLOGY, AND CELL AND MOLECULAR BIOLOGY.

THEIR RESEARCH IN THE BASIC SCIENCES IS ALSO INTIMATELY INTERWOVEN WITH MEDICAL ADVANCEMENTS AND HAS LED TO A BETTER UNDERSTANDING IN A NUMBER OF DIVERSE AREAS. EXAMPLES OF SUCH CONTRIBUTIONS WOULD INCLUDE:

1. IDENTIFICATION OF THE ETIOLOGY OF CERTAIN TYPES OF DIABETES.

2. KNOWLEDGE ON THE PRODUCTION, MAINTENANCE, AND DEGRADATION OF CONNECTIVE TISSUE COMPONENTS SO IMPORTANT IN GROWTH AND DEVELOPMENT, WOUND HEALING, AND THE CHANGES WHICH OCCUR IN THE AGING PROCESS.

3. ELUCIDATION OF THE INFLAMMATORY PROCESSES INVOLVED IN PERIODONTAL DISEASES, AS WELL AS IN THE CRIPPLING CONDITIONS OF ARTHRITIS AND

4. INSIGHTS INTO THE MECHANISMS AND CONTROL OF PAIN.

Dr. LÖE COMES TO US WITH A RICH BACKGROUND OF RESEARCH IN HIS FIELD OF PERIODONTOLOGY, FOR WHICH HE IS KNOWN WORLDWIDE. DURING HIS TENURE AS DEAN OF THE UNIVERSITY OF CONNECTICUT SCHOOL OF DENTAL MEDICINE, HE HAS EXERTED STRONG LEADERSHIP IN BRINGING THAT INSTITUTION TO THE FOREFRONT IN RESEARCH AMONG ALL DENTAL SCHOOLS.

DR. LÖE, THIS NEW CHAPTER IN YOUR DISTINGUISHED CAREER WILL BE A CHALLENGING ONE--BUT YOU CAN BUILD WITH ASSURANCE UPON THE FOUNDATIONS LAID BY YOUR PREDECESSORS. I WISH TO EXPRESS ON BEHALF OF ALL OF US A SPECIAL WORD OF APPRECIATION FOR THE DEDICATION AND ABILITY OF THE NIDR STAFF, PARTICULARLY DR. JOHN GOGGINS, WHO, AS ACTING DIRECTOR FOR THE PAST YEAR, HAS PROVIDED DYNAMIC LEADERSHIP IN THIS THE WORLD'S FOREMOST DENTAL RESEARCH INSTITUTE.

AND NOW, DR. LÖE, IF YOU WILL COME FORWARD, I WILL HAVE THE PLEASURE OF ADMINISTERING TO YOU THE OFFICIAL OATH OF OFFICE. I WILL ALSO ASK MRS. LÖE TO ASSIST.

REMARKS*

INTRODUCTION OF DR. SAMUEL D. PROCTOR

MARTIN LUTHER KING CEREMONY

JANUARY 12, 1983

AS MEMBERS OF A LARGE RESEARCH COMMUNITY, WE ARE REMINDED ALMOST DAILY OF OUR DEBT TO THE MEN AND WOMEN OF SCIENCE IN WHOSE FOOTSTEPS WE FOLLOW. THEIR LEGACY OF KNOWLEDGE AND SCIENTIFIC INSIGHT IS AN INDISPENSABLE RESOURCE FOR TODAY--AND IT IS OUR RESPONSIBILITY NOT ONLY TO PUT IT TO USE, BUT TO ADD OUR CONTRIBUTION TO IT FOR THE BENEFIT OF THOSE WHO WILL FOLLOW.

THIS ANNUAL COMMEMORATION OF MARTIN LUTHER KING'S BIRTHDAY SERVES AS A REMINDER TO EACH OF US OF ANOTHER HERITAGE EVEN MORE VALUABLE THAN SCIENCE, A LEGACY BESTOWED THROUGH THE LIFE AND WORKS OF DR. KING.

DR. KING'S TEACHINGS, SO FORCEFULLY COMMUNICATED BY HIS ACTIONS AND HIS ELOQUENCE, ARE AS TIMELY TODAY AS THEY WERE DURING HIS ALL-TOO-BRIEF LIFETIME.

OTHERS NOW CONTINUE TO PROCLAIM THE SAME TRUTHS. WE ARE FORTUNATE TODAY TO HAVE AS OUR COMMEMORATIVE SPEAKER A LEADING MINISTER AND EDUCATOR WHO ABLY CARRIES ON IN THE MARTIN LUTHER KING TRADITION.

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*Dr. James B. Wyngaarden, Director
National Institutes of Health

DR. SAMUEL D. PROCTOR IS A VIRGINIAN, AN ALUMNUS OF VIRGINIA UNION UNIVERSITY, CROZER SEMINARY, AND BOSTON UNIVERSITY WHERE, IN 1950, HE EARNED HIS DOCTORATE IN ETHICS.

HE BEGAN HIS CAREER AS MINISTER SERVING THE POND STREET BAPTIST CHURCH IN PROVIDENCE, RHODE ISLAND, FROM 1945-1949. DR. PROCTOR WENT BACK TO HIS ALMA MATER, VIRGINIA UNION UNIVERSITY, IN 1949, WHERE HE SERVED AS PRESIDENT FROM 1955-1960, BEFORE A FOUR-YEAR TERM AS PRESIDENT OF NORTH CAROLINA A & T STATE UNIVERSITY. FROM 1964-1969, HE HELD ADMINISTRATIVE POSITIONS WITH THE PEACE CORPS IN NIGERIA AND WASHINGTON.

SINCE 1969, DR. PROCTOR HAS OCCUPIED THE MARTIN LUTHER KING MEMORIAL CHAIR AS PROFESSOR OF EDUCATION IN THE GRADUATE SCHOOL OF EDUCATION OF RUTGERS UNIVERSITY. HE ALSO SERVES AS SENIOR MINISTER OF THE FAMOUS ABYSSINIAN BAPTIST CHURCH OF NEW YORK CITY. IN ADDITION, DR. PROCTOR IS A MEMBER OF THE GOVERNING BOARDS OF THE UNITED NEGRO COLLEGE FUND, MEHARRY MEDICAL COLLEGE, OVERSEAS DEVELOPMENT COUNCIL, MIDDLESEX GENERAL HOSPITAL, NEW JERSEY, AND THE COUNCIL FOR RELIGION AND INTERNATIONAL AFFAIRS. HIS SERVICE TO THE NATIONAL INSTITUTES OF HEALTH INCLUDES MEMBERSHIP ON THE RECOMBINANT DNA ADVISORY COMMITTEE.

DR. PROCTOR HAS BEEN AWARDED ALMOST A SCORE OF HONORARY DEGREES IN RECOGNITION OF HIS ACCOMPLISHMENTS AND SERVICE.

WE ARE HONORED, INDEED, TO HAVE YOU HERE FOR THIS OCCASION, DR. PROCTOR--AND IT IS MY GREAT PLEASURE TO PRESENT YOU TO THIS AUDIENCE OF MEMBERS OF THE NIH COMMUNITY.

NINCDS "ALL HANDS" MEETING*

Remarks

by

James B. Wyngaarden, M.D.**

I am pleased that Dr. Goldstein asked me to stop by today for your annual "all hands" meeting. I am especially pleased that the NINCDS is in such good hands with the appointment of Dr. Goldstein as its director. I am sure that Dr. Goldstein will continue to provide strong leadership to the Institute.

Early in my directorship at NIH I had an opportunity to become familiar with many of the leading research areas in neurology and communicative disorders and with the programs of the NINCDS when I met with members of the National Committee for Research in Neurological and Communicative Disorders. Just a week or so later I chaired the annual Wakeman symposium, sponsored by the Duke University Department of Neurology, and became thoroughly fascinated by the complex area of nervous system regeneration. The progress made over just the last five years in this area is phenomenal and a testimonial to the scientific leadership from NINCDS.

But I am equally impressed with other NINCDS work going on intramurally and extramurally—in the development of non-invasive imaging techniques, in neurobiology, immunology, virology, genetics, enzyme regulation, etc. I am very optimistic about the prospects for achievements in neurological and communicative disorders in the decade ahead.

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*National Institutes of Health, January 13, 1983

**Director, National Institutes of Health, Bethesda, Maryland

As Dr. Goldstein well knows, NIH directors and directors of institutes have numerous occasions to meet with a variety of audiences around NIH and outside of the agency. But I especially want to commend Dr. Goldstein for having this kind of meeting--one which includes the people who count so much in the achievement of our research mission.

Many institutes have such 'all hands' meetings from time to time, but I know of no other Institute that calls in a speaker from outside of the agency to present, perhaps, another view. At times, we become so accustomed to talking with one another that we forget that perceptions of those outside the NIH circle may differ from ours. This new perspective can be both enlightening and encouraging. I will be very interested to hear from the Honorable James Roosevelt, a speaker who can provide a very special view to all of us.

Dr. Goldstein, I would be pleased to take a few questions if the schedule permits.

CEREMONY*
DESIGNATING BUILDING ONE
THE JAMES A. SHANNON BUILDING

Dr. Wyngaarden:

IT IS MY PLEASURE TO WELCOME ALL WHO HAVE COME TO PARTICIPATE IN THIS HAPPY OCCASION AND TO EXTEND SPECIAL GREETINGS TO THE FRIENDS AND FORMER COLLEAGUES OF DR. SHANNON WHO ARE JOINING WITH US IN THIS CELEBRATION.

IF I WERE TO PRESENT ALL OF THE NIH NOTABLES WHO ARE HERE, WE WOULDN'T HAVE TIME FOR OUR PROGRAM, SO I MUST EXERCISE THE CHAIRMAN'S PREROGATIVE AND LIMIT THE FORMAL INTRODUCTIONS TO THE PERSONS ON THE PLATFORM, TO THE THREE FORMER NIH DIRECTORS WHO ARE IN THE AUDIENCE, AND TO THE MEMBERS OF DR. SHANNON'S FAMILY WHO ARE WITH US TODAY --

(List of Former Directors and Platform Guests)

Dr. Wyngaarden:

AS AN AUDIENCE FAMILIAR WITH GOVERNMENT PROCEDURES, YOU NEED NOT BE TOLD THAT AN ACTION LIKE NAMING A MAJOR FEDERAL BUILDING IS NOT TAKEN CASUALLY. ORDINARILY, THE PROCESS OF APPROVAL TAKES ON A LONG LIFE OF ITS OWN. IN THIS INSTANCE, HOWEVER, OUR NOVEMBER 24, 1982, PROPOSAL TO MAKE BUILDING ONE THE JAMES A. SHANNON BUILDING WAS IMMEDIATELY APPROVED AND ACTIVELY ESPOUSED BY ASSISTANT SECRETARY BRANDT AND JUST AS QUICKLY ACCEPTED AND ACTED UPON BY SECRETARY SCHWEIKER.

OBVIOUSLY WE HAD A GOOD CASE BUT, IN ADDITION, WE PRESENTED IT TO AN ASSISTANT SECRETARY FOR HEALTH AND A SECRETARY WHOSE UNDERSTANDING AND SUPPORT OF THE NIH HAVE BEEN CONSISTENT AND EFFECTIVE; WHO HAVE DEMONSTRATED DEEP FEELINGS ABOUT THE PAST, PRESENT, AND FUTURE OF THE AGENCY AND ITS PEOPLE.

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*Warren G. Magnuson Clinical Center, Masur Auditorium, Bethesda, Maryland, January 18, 1983.

IN OUR PROGRAM TODAY, WE WILL HEAR FROM SOME OF OUR HONOREE'S LONGTIME FRIENDS AND CO-WORKERS--WHOSE REFLECTIONS WILL CONVEY THE FEELINGS OF RESPECT AND AFFECTION HELD FOR DR. SHANNON AMONG ALL WHO KNOW HIM AND HIS WORK. BEYOND SUCH PERSONAL FEELINGS FOR AN HONORED COLLEAGUE, HOWEVER, THE APPROPRIATENESS OF THE ACTION BEING TAKEN TODAY IS RICHLY SUPPORTED BY THE RECORD OF HIS ACHIEVEMENTS.

WE WILL BEGIN OUR PROGRAM WITH A FILM OF ANOTHER FESTIVITY HONORING DR. SHANNON SOME SIX YEARS AGO. I THINK YOU WILL ENJOY IT. ON THAT OCCASION, DR. DEWITT STETTEN WAS MASTER OF CEREMONIES . . .

Film Unveiling of Shannon Bust

Dr. Wyngaarden

NOW WE ARE TO HEAR FROM THE MEMBERS OF A MOST UNUSUAL AND DISTINGUISHED PANEL OF SCIENTISTS. SO DISTINGUISHED, IN FACT, THAT THE USUAL INTRODUCTION FOR EACH IS NEITHER NECESSARY NOR WOULD IT BE POSSIBLE IN ANY REASONABLE LENGTH OF TIME.

THE FIRST SPEAKER IS DR. DEWITT STETTEN -- "HANS"

Dr. Stetten Reflections

Dr. Wyngaarden

NEXT, DR. SIDNEY UDENFRIEND - "SID"

Dr. Udenfriend Reflections

Dr. Wyngaarden

AND NOW DR. ROBERT BERLINER - "BOB"

Dr. Berliner Reflections

Dr. Wyngaarden

WE WILL NOW HEAR FROM DR. CHRIS ANFINSEN - "CHRIS"

Dr. Anfinsen Reflections

Dr. Wyngaarden

AND NOW DR. JULIUS AXELROD - "JULIE"

Dr. Axelrod Reflections

Dr. Wyngaarden

OUR LAST PANELIST IS DR. BERNHARD WITKOP - "BERNIE"

Dr. Witkop Reflections

Dr. Wyngaarden

IT IS NOW MY PLEASURE TO INTRODUCE DR. EDWARD BRANDT, ASSISTANT SECRETARY FOR HEALTH, FOR A SPECIAL PRESENTATION.

Dr. Brandt Remarks and Official Designation of Shannon Building.

Dr. Wyngaarden

AND NOW, DR. SHANNON--

Dr. Shannon Response

Dr. Wyngaarden

THE RECEPTION WHICH WILL FOLLOW IMMEDIATELY WILL PERMIT EACH OF US TO CONTINUE THE REFLECTIONS, GREETINGS, AND CONGRATULATIONS THAT HAVE ONLY JUST BEGUN. THE SIGNS IN THE HALL AT THE BACK OF THE AUDITORIUM WILL LEAD US TO THE ACRF CAFETERIA BALCONY WHERE THE RECEPTION WILL BE HELD.

THANK YOU.

STATEMENT*

James B. Wyngaarden, M.D.**

After eight months as Director of the National Institutes of Health, and in this, my first formal meeting with the Advisory Committee, I thought it appropriate to discuss with you some early impressions of current operations and policies, to look ahead, and, finally, to consider how this Committee might be most useful in our efforts.

There has never been a blueprint for the development of NIH, nor for the growth of the American biomedical research enterprise into the productive collaboration among government, academia and industry that exists today. The system grew in response to challenges and opportunities as they arose; its achievements have contributed to better health for more people than ever before, and to the prospect of even greater health benefits. This pragmatic approach will continue to serve us well as we face new conditions, new challenges and new opportunities. It is these challenges and opportunities that I propose to discuss with you today.

Perspective

Each Director of NIH is confronted by a unique set of circumstances created by the evolution of science, technological developments, the changing expectations and priorities of the public as expressed by the Administration and Congress, and by economic conditions. The shaping of NIH from its origins in the Laboratory of Hygiene of 1887 demonstrates this fact: the agency responded through the years to needs and opportunities as perceived internally and by diverse groups, within and outside Government. I will not chronicle the step-by-step evolution of NIH into its present 16 Institutes, Divisions and Bureaus, but I think a brief summary of the past will provide perspective for our deliberations today.

Although from the late nineteenth century to the 1930s it was recognized that scientific research could contribute effectively to the solution of health problems, the role of the Federal Government in biomedical research and medical education was minimal. Private foundations, voluntary organizations, and professional societies were the dominant sources of support and influence in shaping the health science endeavor.

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* Presented at the convening of the 46th Meeting of the Advisory Committee to the Director, NIH, at the National Institutes of Health, Bethesda, Maryland, January 19, 1983.

**Director, National Institutes of Health.

The science of medicine was slowly developing after the turn of the century, but it was not until the decade 1935-1945 that what we term "modern medicine" had its beginning; when the discovery of sulfonamides and penicillin enormously increased the ability of physicians to intervene successfully in the control of disease. Concurrently, the Federal Government began to play a greater role. The Laboratory of Hygiene was moved from Staten Island to Washington and named the National Institute of Health in 1930, and seven years later, the National Cancer Institute was established as a separate and coordinate entity.

Congress declared its belief in the importance of health research in the Public Health Service Act of 1944, of which Section 301 gave a broad charter for the conduct of biomedical research in directing the Surgeon General to:

> . . . conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man. . . . (1)

The 1944 Act established the legislative basis for future developments and provided for the association of the National Institute of Health with the National Cancer Institute. The 1940s also saw the establishment by Congress of the National Heart Institute, the National Institute of Dental Research, and the National Microbiological Institute, and the change of the agency's name to the National Institutes of Health. NIH turned outward to the research community while expanding and strengthening its intramural base. Under the Directorship of Dr. Rolla E. Dyer, the Division of Research Grants was organized, laying the foundation for today's extensive extramural program. His successor, Dr. William H. Sebrell, Jr., saw to the opening of the world-renowned Clinical Center.

The time was ripe for rapid and massive expansion of NIH and its programs, in organization and funding, and in the science base, when Dr. James A. Shannon became Director in 1955. The budget of the Agency was then $82 million and when he retired 13 years later, the budget had topped $1 billion. During Dr. Shannon's tenure, NIH became virtually complete, only three more Institutes being added later.

Under Dr. Shannon, many of the current mechanisms of support for biomedical science were established, confirmed and extended. They have served us well. Dr. Shannon insisted that the Congressional mandates to conduct research in cancer, heart disease, and arthritis, for example, be interpreted broadly. He realized that the science base was not sufficient to permit a frontal assault on the diseases themselves. He set about to build the research capability of this country, through the intramural program here in Bethesda and through a substantial expansion of the mechanism of grants-in-aid to institutions. Biomedical communication was enhanced when the National Library of Medicine, then a separate bureau, became part of NIH. Corollary objectives included the strengthening of the institutions in which biomedical

research would be done, and the development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and the brightest young minds in the universities. Together with Hill-Burton money for clinical facilities, NIH construction funds for research facilities modified the topography of the academic medical center and indirectly changed and strengthened medical education.

During Dr. Shannon's tenure, the Federal Government, through NIH, became the primary source of support for biomedical science in the United States. His contributions to the development of NIH and to the research enterprise were recognized once again yesterday when Building One on this campus was named in his honor.

The next period, under the direction of Drs. Robert Q. Marston and Robert S. Stone (1968-1975), was one of consolidation and refinement of programs and procedures. It saw the addition of three new Institutes and reorganization of others. The period was also marked by a combination of reduction and growth. There was an OMB decision to reduce or eliminate, throughout the Federal Government, funds for research training and institutional support. The funds were later restored by Congress. At the same time, under statutory mandates in 1971 and 1972, the National Cancer Institute and the National Heart Institute developed notable research strategies and assumed responsibility for community outreach programs. The cancer program surged more fully into the mainstream of academic medicine as major cancer centers were developed and program ties were strengthened with most leading academic science institutions. The Cancer Institute budget increased rapidly and the over-all annual NIH budget exceeded $2 billion during the Marston-Stone years.

Then came the tenure of Dr. Donald S. Fredrickson (1975 to 1981) when the full force of the biological revolution was felt and scientific opportunity abounded. The appropriations for NIH continued to grow and exceeded $3 billion for the first time. But other forces were at work and the growth in support was more apparent than real--the 1979 appropriation of $3.2 billion being worth only $1.62 billion in terms of 1969 dollars, an all-time high in constant dollars. The steady rise in the flow of constant dollars then began to decline: in 1980 to $1.6 billion and to $1.55 billion in 1969 dollars during 1981. (Interrupting the chronology here to bring you up to date, I should note that, in terms of 1969 dollars, 1982 saw a further dip to $1.4 billion, and in 1983 we expect a slight increase to $1.5 billion. The decline in purchasing power seems to have leveled off.)

The time had come for a reassessment of programs and policies in order to maintain the momentum of scientific inquiry in the face of a decline in purchasing power. The answer was a policy of stabilization which recognized and articulated a trend already evident during the mid-1970s. This policy was designed to maintain a steady and predictable level of support for investigator-initiated research projects and the training of new investigators while continuing to carry out other important responsibilities. These responsibilities, which continue today, include support for research centers

and research resources, biomedical communications, international activities, clinical trials, and emphasis on prevention of disease and promotion of health.

Dr. Fredrickson also recognized growing public concern over certain areas of health research, and NIH responded by increasing the participation of public members in agency deliberations. He provided the impetus that led, for example, to guidelines for work with recombinant DNA, the National Toxicology Program, and to data collection and analysis of the health impact of ionizing radiation.

And that brings us to the present. Public expression of confidence in the potential of health research, together with a multi-billion-dollar investment through the years, built a biomedical research capacity second to none. It is a source of national pride and international prestige, a health resource that benefits people in this country and throughout the world. We have inherited a tradition of achievement and excellence. A strong research community is in place. The fundamental NIH policies, programs and procedures provide a firm foundation upon which to build.

However, new times call for new approaches. One of the strengths of our research system is its ability to accommodate change and seize opportunity. Our primary challenge is: how best to capitalize on the vast scientific opportunity before us during a time of constrained resources. The budget for biomedical research, more specifically that of NIH, cannot be expected to grow substantially in the immediate future. But it is a very large budget, about $3.6 billion in fiscal year 1982 and more than $4 billion in the current fiscal year. It is a budget that confirms the support of Congress and the Administration for biomedical research, but we are in a budgetary steady state and are likely to be so until there is a substantial improvement in the economy.

Several adjustments will be necessary if we are to secure the greatest amount of the best science within available resources. We will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration. We will also have to manage and administer our programs most efficiently so that we can take advantage of research opportunities.

NIH Mission and Principles

Programs, policies and priorities of NIH have been modified and expanded through the years, but the fundamental mission and principles of the agency have not changed during the modern era. The mission of NIH is a broad one that can be simply stated: "to uncover new knowledge that will lead to better health for everyone."

The President's Biomedical Research Panel in its 1976 Report stated it this way:

> The primary mission of the NIH, as constituted today, is fostering, supporting, and conducting laboratory and clinical research to increase our understanding of life processes and the etiology, treatment, and prevention of disease. (2)

In carrying out that mission, certain principles evolved at NIH that will continue to guide our decisions.

One principle is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to eventual triumph over disease and suffering.

The rationale for this approach was well stated by the President's Panel:

> Before there can be intelligently conducted applied research, before there can be demonstrations or clinical trials, or before there can be public dissemination of techniques, there must be enough productive basic research to provide the fundamental science from which these efforts flow. (3)

As to Government's responsibility to support fundamental research, Dr. George Keyworth, the President's Science Advisor, put it this way: "Basic research warrants government support because it is an investment in the future--in a better quality of life, better security, a better economy, and simply better understanding." He went on to emphasize that basic research is a responsibility of government for the dual reasons that it benefits the people and the economy, and that there is no other source of support for basic research on the scale required. (4)

A second fundamental principle is that investigator-initiated research holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period.

A third element of these timeless principles is that there is a need to assure a continuing supply of well-trained scientists to carry out research to meet national health goals. There is a close inter-relationship between the continued productivity of research and the availability of qualified investigators.

A fourth principle is that the primary means for pursuit of basic research is the academic community, that being where the majority of scientists are to be found. NIH has proceeded on a course that, in many ways, was charted in a report written by another Science Advisor to the President, Vannevar Bush.

His 1945 report, entitled "Science--the Endless Frontier," stands up in sturdy perspective when viewed with the critical hindsight of nearly 40 years. Bush said:

> The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. . . . (5)

* * * * *

> While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any extension of medical facilities must be accompanied by an expansion of medical training and research.
>
> Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences. (6)

A final principle is that of public accountability--by Government and by recipients of Government support. It is the responsibility of NIH to protect the massive public investment in health research through adherence to both the letter and the spirit of the laws under which it operates. NIH has a very specific health mission which amounts to a social contract to foster the advance of biomedical research for public benefit. We support fundamental research within the overriding objective of ultimate contribution to the prevention and cure of illness.

Our responsibility to the public interest extends to awardees and contractors who receive NIH support for their work. We must assure, of course, that public funds are appropriately used for public purposes. Those who receive NIH support must conduct their work in accord with the highest scientific rigor and make certain that ethical standards are observed, in regard to the rights of human subjects, the humane treatment of animals in research, and the use of new technologies, for example. It is also our responsibility to see that new knowledge is brought into medical practice as rapidly as appropriate.

Issues and Challenges

We must adhere to those principles as we establish priorities and policies to carry out the mission of NIH. As conditions change, however, we may want to reconsider how they are applied. There are several areas of concern and a number of issues to be resolved during this decade so that the pace of inquiry can be maintained, the knowledge base increased, and research findings transferred to medical practice in a timely fashion.

Among the major issues for our consideration is one that undergirds all the others: the need to preserve the integrity and strength of NIH itself. In the coming years, we must make certain that the structure and policies and programs of NIH are able to meet the changing demands of biomedical science. I said earlier that the development of NIH was shaped by the agency's response to challenges and opportunities presented by scientific, social and economic conditions. As the knowledge base expands rapidly and its potential for the conquest of chronic disease is more widely recognized, we can expect mounting pressure to focus narrowly on specific diseases and organ systems. This motivation is understandable, but is it the best way to support the evolution of science? Given the state of biomedical research today and its potential, it is essential that we be ready to attack the many interrelated scientific problems before us in the most effective manner possible. As a step in that direction, we have initiated a study through the Institute of Medicine of the National Academy of Sciences to provide the data we need to make strategic decisions in the future. I will have more to say about this subject, and how this Committee can contribute to its analysis, in a few moments. I bring up this subject now so that it will be in your minds as we discuss other issues and challenges.

I would like to identify four major issues for consideration in terms of the NIH mission and our basic principles:

- The development of priorities that will maintain the strength of the research enterprise. This involves issues of scientific opportunity, funding mechanisms, renovation of physical facilities, and scientific instrumentation.

- Training the next generation of investigators. Here, we need to find better ways to link training efforts to scientific opportunities and to encourage the entry of new investigators, including clinical researchers.

- Stretching the research dollar without compromising quality. We have received numerous suggestions, such ideas as including a sliding scale for support and the limiting of support to individual scientists.

- The clarification of Federal/institutional relationships. There are several issues, such as indirect costs, salary support on grants, and mechanisms of accountability to be considered.

In terms of setting our priorities, I consider the primary issue to be that of stabilization. The stabilization policy makes a powerful statement to the extramural community. It says that NIH is doing its utmost, consistent with program balance and Congressional mandates and directives, to assure that the best research will be adequately funded, that young scientists will have opportunities in research, and that we will protect their entry into the research enterprise--not out of charity but because the vitality and success of the research endeavor depends on them. About 50 percent of all awards in recent years for new traditional research projects (R01) are made to scientists who have never before been principal investigators. Thus about

12 percent of our total portfolio of some 16,000 grants is in the hands of scientists in their first year as a principal investigator.

Under stabilization, investigator-initiated research projects and research training have been given top priorities. In order to maintain essential research programs, and to reduce the turbulence of the system, NIH has sought to fund 5,000 new and competing renewal research grant awards and 10,000 trainees each year. The report on the continuing resolution for FY 1983 said: "The conferees continue to believe that basic research and stable funding for investigator-initiated research grants are of the highest priority. With the funds provided, NIH should support as close to 5,000 new and competing research project grants as possible." (7) In separate reports, House and Senate Appropriations Committees also expressed strong support for research training. (8)

But the stabilization policy also has its down side. In order to fund 5,000 new and competing projects, dollars have been shifted from other mechanisms in recent years. While the proportion of the NIH budget assigned to support investigator-initiated research projects has grown, other mechanisms have been curtailed, especially NIH initiatives to emphasize special areas or activities, as in centers and other programs sought through RFAs, or to answer specific questions, as in clinical trials and other activities sought through contracts. It has also indirectly exerted pressure on our commitment to support research projects for the life of the award period. After several turns of the ratchet, many Institute Directors feel that further shifts would seriously limit their ability to meet other program goals and to maintain program balance. If the rate of increase in percent of the NIH budget devoted to the extramural grant component were to continue, it would reach 100 percent in 1993.

During the past year, questions have been raised about the size of the intramural research program. The program decreased from 28.6 percent of the NIH budget in 1955 to about 12 percent for several years, but recently it rose to 13 percent at a time when the proportion for extramural support was dropping. This is an investment that continues to pay off in many ways. Productivity of the program can be measured in the breadth and quality of research publications, number of Nobel laureates, and preeminence in research leadership, such as recombinant DNA technology. A recent assessment of biomedical research institutions based on number and impact of publications placed the NIH intramural program and Harvard University at the top of the list. The intramural training experience has equipped hundreds of young basic scientists and clinical investigators to assume research and leadership roles at universities in this country and around the world. The program is flexible and accommodates studies that require years of uninterrupted investigation and support, such as studies of slow viruses. Many of the mechanisms and techniques for awarding grants and subsidizing training were developed in the intramural program.

There is also the question of the Warren G. Magnuson Clinical Center which, with its new Ambulatory Care Research Facility, is a unique and productive blending of fundamental and clinical research with both inpatients and outpatients. It is no surprise that the Clinical Center, like other

hospitals, faces the problem of rising costs, currently in the range of 15 to 17 percent annually. The 1983 budget allows for only a 9 percent increase for NIH which means that a shortfall in Clinical Center operating costs must be made up from other internal sources.

It is questions of this type--the setting of priorities among essential and vital activities while maintaining stability in the research and training base--that we must resolve.

We also need to take a closer look at how we respond to and capitalize on scientific opportunities. Toward this end, the central NIH planning process has been modified this year to provide a greater focus on the substance of science. The planning sessions between the NIH Director and BID leadership are being devoted to detailed discussions of emerging scientific opportunities and areas of high scientific priority. The results of these discussions will provide a substantive context within which decisions will be made on the allocation of NIH resources. These review sessions also provide an opportunity for identification and discussion of areas of research which cut across traditional organizational lines.

In order to support this work, we will have to pay special attention to the research resources that maintain the quality of the environment in which modern biomedical research is performed. The excellence of science today depends on essential but costly resources, such as sophisticated instrumentation that utilizes new technologies, clinical research centers for the application of laboratory advances to human health care, large capacity computers for the analysis of data, and centers for the development and breeding of colonies of unique animal models critically needed for the study of human disease. We will continue to seek ways to revitalize the Nation's instrumentation base and other resources needed to conduct biomedical research.

A second major area of concern is the training of the next generation of scientific investigators who are essential to the continued vigor of inquiry. NIH has sought to provide stable support for research training programs. Some 10,700 trainee positions were supported in 1981 and 10,400 last year. This year, we expect to support almost 10,000 trainee positions. We are working closely with the National Academy of Sciences to identify needs and match them with opportunities in science. We realize it is difficult to quantify such activity, but it is important to reduce the wide swings experienced in the past.

One subject of special concern is the present and future state of clinical research. A burgeoning of fundamental knowledge in the past decade has opened up vast opportunities for clinical research. Nevertheless, a diminishing proportion of physicians are interested in applying themselves to the clinical research needs of tomorrow. Some quantitative data may serve to emphasize the points to be made. There was a decline in the number of M.D.s holding research project awards from about 3,400 in 1968 to about 2,500 in 1973. Since that time the number has increased slightly but in 1980 it was still below 3,000. The percentage of grants held by M.D. principal investigators dropped from about 35 percent of all research grant awards in 1968 to about

23 percent in 1980. During the same time, the percentage of grants held by Ph.D. principal investigators increased from 52 to 67 percent. The percentage held by M.D.-Ph.D. principal investigators has remained nearly steady at about 10 percent of the total.

In my view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science.

We are also considering approaches and initiatives to encourage M.D.s to enter into or remain in research careers and to improve their effectiveness. For example, at the undergraduate medical student level, we continue to give the Medical Scientist Training Program top priority in our training portfolio and the National Research Service Award permits short-term training of medical students. And I should point out that the NIH intramural research program provides training for many clinical investigators.

This growing problem has also received considerable attention in the Congress. Last fall, for example, we received the Report of the House Committee on Appropriations regarding the proposed 1983 budget for NIH. (9) The Committee noted that young physicians are often dissuaded from applying for research training or fellowships because they perceive instability in the Federal commitment to research and because of their awareness that a research career represents a substantial financial sacrifice when compared to almost any form of medical practice. The Committee asked NIH to review the problem and report back at hearings this year. Even without that prodding, we have devoted considerable attention to this issue and have under consideration some major steps toward its solution. You will hear more about steps we are taking and considering to resolve it later today.

Another major issue facing us is the need to stretch the research dollar without compromising the quality of investigation. This need has created anxiety in the research community and has prompted varied responses, in my view largely constructive. In public testimony and private correspondence, scientists and administrators have impressed upon Congress the need for strong support for biomedical research.

During 1982, although we funded 5,027 new and competing research project awards, this figure represents only about a third of approved grant applications. The priority scores of those awarded cut off at 160-180 in most cases. While we share a deep concern for scientists whose deserving projects we cannot fund, we feel that the interests of science are best served by funding the most meritorious work as judged by the peer review system, and by assuring that such projects are funded prudently yet adequately for the execution of the study.

In the search for ways to fund greater numbers of projects, some have suggested a limitation of the dollar support awarded to any individual

principal investigator. This proposal has taken several forms. One would limit the number of dollars per project or per laboratory. Another is to limit the number of grants in the name of any principal investigator. At present about 10 percent of principal investigators have two or more traditional research project grants.

A third proposed mechanism, which has received some support, is that of a sliding scale in the payment of approved awards. It is suggested that NIH fund grants of the very highest priority scores at 100 percent of the award rate, the next category at 90 percent, followed by 80 percent, 70 percent, and so on. We have examined this concept very carefully but find it flawed in several particulars. As we have reviewed alternatives for spreading research dollars across a larger number of investigators, we have found ourselves reaffirming the traditional practice of awarding grants on the dual bases of scientific merit and program relevance, as determined by study section and council review.

Another important area of continuing concern is the relationship between the Federal Government, or NIH, and the biomedical research community. Our collaboration has grown steadily closer since the beginning; the relationship is strong and productive. It is essential that the Federal partnership with academia and other research institutions remain vigorous and healthy because, as we are all aware, the search for fundamental knowledge and the development of scientists can best be conducted by these institutions. The relationship has been tested many times and problems have been solved through open and candid discussion. I am confident that we will overcome today's problems by following the same course. Among the subjects attracting our attention at present are indirect cost reimbursement, salary support, and mechanisms by which we jointly govern the research enterprise.

Let me define the problem of indirect costs as seen by the NIH. Prior to 1966, NIH paid a flat rate of 8 percent, then 15 percent and, finally, 20 percent of the total award to cover indirect costs of a research grant. The Wooldridge Report of 1965 recommended that NIH abandon the flat rate, and instead pay a negotiated rate of indirect costs based on audits. For the next six years the average indirect cost rate rose rapidly, and by 1972 amounted to 21 percent of the total research grant dollar. Since that time it has risen less sharply but at a steady rate each year, reaching 30 percent of the total dollar in FY 1982. Put another way, for each dollar of direct costs, 43 cents go to indirect costs. This inexorable rise of the total fraction of the research budget represented by indirect costs has occurred irrespective of the rate of change of the research budget. In virtually every one of the last 16 years, the indirect cost rate has grown faster than the direct cost rate.

The issue has been raised to a high level of visibility by the responses of university administrators to the Congress. Administrators are understandably concerned about the solvency of their institutions, and emphasize that indirect costs are true costs of research, a point we do not contest. Congress is concerned about the rate of growth of indirect costs and in the current continuing resolution has provided additional funds for full payment of indirect costs. However, in its report on the proposed 1983 budget, the House Committee on Appropriations has asked for two studies of

indirect costs, one by the Department of Health and Human Services, another by the Comptroller General. (10) At issue is the containment of indirect costs, and the extent of cost sharing between the universities and the Federal Government. This has become a divisive issue which requires early resolution. The 1983 proposal of paying only 90 percent of negotiated rates was, as you know, rendered unnecessary by Congress when it added funds sufficient to pay full indirect costs. Such a proposal is clearly not a long-term solution, and indeed it was proposed only as an interim device. This Committee has devoted considerable effort to this question and the data gathered, along with the record of deliberations, will serve us well as we continue to consider the problem of indirect costs. I hope that a satisfactory resolution of this matter will be developed within the next year.

Another issue that we are currently examining is the trend in the salary support of principal and other investigators as a percentage of the research award. We need more data to learn whether new responses to the latest accountability requirement of circular A-21 have led to significant shifts in this category. We recognize that this is a complex and sensitive issue, but we feel it requires assessment.

In addition to such fiscal considerations there are questions of the mechanisms of accountability to be reviewed; for example, policies concerning the protection of human subjects in research, the care and use of animals in research, and alternatives to the use of animals in toxicological testing. As biomedical research delves deeper into life processes and the manipulation thereof, through recombinant DNA technology and genetic engineering, for example, we are increasingly faced with questions in the areas of ethics, economics and public policy. Also, the apparent increase in the number of instances of misconduct in science has generated concern and alarm within the scientific community and the general public. We are still developing mechanisms for handling this issue both at the institutional and NIH levels.

Addressing the Issues

That is a lengthy agenda of issues, all of them difficult and complex; an agenda too large to be considered in full at one sitting by the Advisory Committee. Among the most pressing are the pursuit of stability and maintenance of momentum and quality; the training of investigators, especially clinical researchers; and institutional relations, between NIH and academic and other research institutions and within those institutions.

This Committee and, indeed, many of you have participated in discussions of these topics. In fact, over the past several years, DAC Working Groups have thoroughly reviewed the costs of biomedical research and the nature of relationships between NIH and the research community. We have acted on a number of your recommendations.

I now propose that we adopt a more focused approach and that the Committee deliberate on a single, broad issue at each of our future meetings. We would, for example, identify a priority issue from among those summarized in the context of policy development at NIH. Our staff would carry out the studies and gather the documentation necessary for informed discussions. The staff

work would be in response to questions raised by this panel as a whole, or from individual members who are concentrating on a specific area or some aspect of a larger issue. To illustrate, let me mention briefly some areas we are now studying, or are preparing to review, and upon which we will have new data for possible consideration by this panel in the future.

As I said, one overriding issue is the organizational structure of NIH and recurring proposals for additional categorical, disease-specific Institutes. Given the many still-unsolved disease entities, there are many possibilities for creation of categorical institutes and good arguments for and against such proposals. The current approach has been highly successful in the past, but modern biomedical research focuses increasingly on the underlying processes of sickness and health, less so on the symptoms of specific disease entities. It is from such deeper understanding of the life processes that we can expect the most important preventive and therapeutic achievements in the years ahead.

Questions about the effectiveness of the NIH organization have been raised in the past. The Wooldridge Committee said in its 1965 Report: "Although there are practical reasons for such an over-emphasis on disease categories in the organizational structure, it is not ideally suited to the kind of research programs which must actually be carried out." (11)

Similarly, the President's Biomedical Research Panel noted in its 1976 Report that the structure creates "two challenges to management: (1) an ever-increasing span of control for the Director, NIH, and (2) a need to assure that this structure does not inhibit interdisciplinary research at a time when all aspects of research, whether fundamental or applied, are increasingly interrelated." (12) The Report added:

> The panel feels that the creation of additional Institutes is not likely to make the NIH more effective; it might well make it less so. Therefore, if new programs are to be established, or existing programs strengthened, this should be accomplished through the present Institutes rather than through the creation of new ones.

As you know, a study of NIH organization was considered during the last session of Congress. The question has also prompted concern within the Department of Health and Human Services. Accordingly, at the direction of the Assistant Secretary for Health, Dr. Brandt, we have initiated a study of the existing organizational structure of NIH and criteria for future change. The study will be conducted by the Institute of Medicine over an 18-month period. The goal of the study will be to examine the adequacy and efficiency of the present structure and to develop a set of criteria--concurred in by the biomedical research community, Congress and the Administration--upon which to determine the need for change, in any substantial manner, of the organizational structure of NIH. Under such criteria, proposals for change could be considered and judged in a more rational and systematic manner than heretofore. The fundamental question is: how can the organization of NIH best serve the continuing evolution of the health sciences?

I have asked two members of the DAC--Drs. Kornberg and Danforth--to serve as consultants to the NIH group which will review and monitor the contract

with the Academy. I would like the other members of the Committee and those of you representing the Advisory Councils to consider carefully your views on this important issue and be prepared to respond to the Academy. I expect to convene this group when the study is complete for a thorough discussion of its findings and implications.

We have selected three topics for more detailed examination today.

The first presentation will describe in some detail the history and pattern of support for biomedical research by NIH. It is intended to provide you with background information for a discussion of stabilization, its continued utility as a major policy, and its impact on other funding mechanisms, and on programs and grantees.

In a presentation on training of investigators, you will be briefed on several evaluations and studies of this subject now under way or being planned. We should consider, for example, whether there is still a need for predoctoral training support, what stability in training implies for individual disciplines, and what are trade-offs resulting from increased financial support for M.D.s entering research.

A third subject for presentation today is the area of clinical trials, in the context of stabilization and its impact on other mechanisms of support for health research. Clinical trials constitute the final step in the testing and validation of medical interventions, and ideally should be performed on each new preventive or therapeutic modality before its introduction into the general body of clinical practice. A scientifically rigorous trial, however, is so demanding of staff, patients, time, and resources that this ideal cannot be realized for each and every medical innovation, only for those of the greatest importance and potentially widest applicability. The questions that we confront with respect to clinical trials include: What is the proper relationship of clinical trials to the more fundamental processes of innovation? Should NIH establish a mechanism for assigning priorities to major clinical trials among, as opposed to within, Institutes and are there reliable alternatives to formal clinical trials for the testing and evaluation of new medical technology?

Data from studies such as these, and special analyses in response to inquiries from members of the Committee, will be made available for consideration in connection with topics selected for deliberation. NIH Bureau, Institute and Division leadership will be involved in the process of issue selection and development. In addition, the scope of information exchange and communication will be extended to Institute Advisory Councils, representatives of which are sitting with us today.

I expect that after the presentations today and further discussion, we can arrive at a list of issues most appropriate for further in-depth consideration by the Advisory Committee during the coming months and at our next several meetings.

In conclusion, I want to emphasize that I look forward to receiving the advice and counsel of this Advisory Committee as we work to achieve our goals.

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12. President's Biomedical Research Panel, p. 15.

REMARKS*

Reception

Dr. Harald Loe, Director
National Institute of Dental Research
January 25, 1983

FIRST, I WISH TO EXPRESS MY APPRECIATION TO DR. MECKLENBURG FOR ARRANGING THIS RECEPTION TO HONOR DR. LOE AND TO GIVE HIM THE OPPORTUNITY TO MEET SOME OF THE PROFESSIONAL AND ADMINISTRATIVE LEADERS WITH WHOM HE WILL BE WORKING.

AT DR. LOE'S SWEARING-IN CEREMONY, JANUARY 10, I SPOKE OF MY PRIDE AND SATISFACTION AT BEING ABLE TO INSTALL HIM AS DIRECTOR OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH.

IT IS WITH THAT SAME PRIDE AND SATISFACTION THAT I COMMEND HIM TO YOU AS A COLLEAGUE.

DR. LOE COMES TO HIS NEW POSITION WITH A RICH BACKGROUND OF RESEARCH IN HIS FIELD OF PERIODONTOLOGY FOR WHICH HE IS KNOWN WORLD WIDE. DURING HIS TENURE AS DEAN OF THE UNIVERSITY OF CONNECTICUT SCHOOL OF DENTAL MEDICINE, HE EXERTED STRONG LEADERSHIP IN BRINGING THAT INSTITUTION TO THE FOREFRONT IN RESEARCH AMONG ALL DENTAL SCHOOLS. I PREDICT THAT HIS TENURE AS THE FIFTH DIRECTOR OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH WILL BE SIMULARLY EFFECTIVE.

AS YOU KNOW, NIDR IS ONE OF THE SENIOR COMPONENTS OF THE NIH. IT WAS THE THIRD INSTITUTE TO BE ESTABLISHED, HAVING BEEN AUTHORIZED IN 1948. FROM THE BEGINNING, NIDR HAS BEEN AN EFFECTIVE PARTNER WITH ALL COMPONENTS OF THE NIH AND WITH OTHER FEDERAL RESEARCH

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*Dr. James B. Wyngaarden, Director,
National Institutes of Health

ACTIVITIES, SOME OF WHICH ARE REPRESENTED HERE TONIGHT. I FEEL SURE THAT THE EXISTING RELATIONSHIPS WILL BE CONTINUED AND STRENGTHENED.

FURTHER, I BELIEVE YOU WILL ENJOY WORKING WITH DR. LOE. HE HAS VERY QUICKLY BECOME A HIGHLY REGARDED MEMBER OF THE ADMINISTRATIVE LEADERSHIP OF THE NIH.

YOU CAN PUT ME AT THE TOP OF THE LIST OF PEOPLE WHO ARE MORE THAN DELIGHTED THAT DR. LOE HAS JOINED OUR PROFESSIONAL AND SCIENTIFIC COMMUNITY.

"SUPPORT OF THE BIOSCIENCES AND THE ZERO-SUM GAME"*

by

JAMES B. WYNGAARDEN, M.D.**

I CONSIDER IT A PRIVILEGE, DR. WAKIL, TO PRESENT THE 11TH "SCIENCE AND SOCIETY" LECTURE IN THE DISTINGUISHED SERIES HONORING VERNA AND MARRS MCCLEAN. THE CONTRIBUTIONS THAT HAVE BEEN MADE TO SCIENCE AND MEDICAL EDUCATION THROUGH THE GENEROUS SUPPORT OF THE MCLEAN FAMILY AND THE MCLEAN FOUNDATION WILL CONTINUE TO BEAR FRUIT FOR MANY YEARS TO COME IN SIGNIFICANT WAYS. THEREFORE, I CONGRATULATE YOU ON THE ESTABLISHMENT OF THIS ANNUAL LECTURESHIP TO MEMORIALIZE THEIR IMPORTANT CONTRIBUTIONS.

AFTER LOOKING OVER THE LIST OF LEADERS IN AMERICAN BIOMEDICAL RESEARCH WHO HAVE APPEARED IN THE PRECEDING LECTURES, I FEEL ESPECIALLY HONORED TO HAVE BEEN INVITED TO PARTICIPATE IN THIS SERIES.

ONE DOES NOT FOLLOW PHILIP HANDLER, LEWIS THOMAS, ARTHUR KORNBERG, FRANCIS CRICK, CARLETON GAJDUSEK AND OTHER DISTINGUISHED SCIENTISTS WHO HAVE PRESENTED THE SCIENCE AND SOCIETY LECTURES WITHOUT A CERTAIN SENSE OF TREPIDATION.

BUT I AM AT HOME IN A MEDICAL SCHOOL. IT IS A FAMILIAR AND CONGENIAL ATMOSPHERE TO ME, AS I WAS PRIVILEGED TO SERVE FOR 25 YEARS AT THE DUKE UNIVERSITY MEDICAL SCHOOL. FURTHER, THE TOPIC OF MY DISCUSSION IS ONE WHICH SHOULD BE OF PARTICULAR CONSEQUENCE IN THIS SETTING—AN OUTSTANDING CENTER OF ACADEMIC TRAINING AND BIOMEDICAL RESEARCH.

THE TITLE OF MY TALK, "SUPPORT OF THE BIOSCIENCES AND THE ZERO-SUM GAME," COULD BE PARAPHRASED AS A QUESTION—"HOW DO WE MAINTAIN THE MOMENTUM THAT HAS LED TO THE CURRENT REVOLUTION IN THE BIOSCIENCES?" - OR "HOW BEST CAN WE CAPITALIZE ON VAST SCIENTIFIC OPPORTUNITY DURING A TIME OF RESTRAINED RESOURCES?" INEVITABLY SUCH A DISCUSSION MUST GIVE MAJOR CONSIDERATION TO THE FEDERAL ROLE--AND FOCUS ON THE NATIONAL INSTITUTES OF HEALTH. THE FEDERAL GOVERNMENT IS THE SOURCE OF AN ESTIMATED 90 PERCENT OF ALL SUPPORT FOR BASIC BIOMEDICAL RESEARCH IN THIS COUNTRY. OVER 60 PERCENT OF HEALTH RESEARCH AND DEVELOPMENT ACTIVITIES AT AMERICAN UNIVERSITIES AND MEDICAL SCHOOLS ARE FUNDED BY THE NIH.

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*Presented at the 11th Annual McLean Lectureship in Biochemistry, Baylor College of Medicine, Houston, Texas, February 7, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

FOR BACKGROUND IT IS INTERESTING TO CONSIDER THE RELATIVELY BRIEF HISTORY OF THE FEDERAL-ACADEMIC PARTNERSHIP THAT HAS BEEN SO PRODUCTIVE IN THE REALM OF BIOMEDICAL AND BEHAVIORAL RESEARCH.

FROM THE PERSPECTIVE OF THE HEALTH SCIENCES AND BIOMEDICAL RESEARCH, THE ACTIVE PARTNERSHIP OF THE FEDERAL GOVERNMENT AND ACADEMIC SCIENCE BEGAN IN 1940, WHEN IN ORDER TO INITIATE AND SUPPORT SCIENTIFIC RESEARCH ON MEDICAL PROBLEMS AFFECTING THE NATIONAL DEFENSE, THE GOVERNMENT TURNED TO THE ACADEMIC SECTOR. BY LATE 1944, THERE WERE ALMOST 500 FEDERAL CONTRACTS FOR MEDICAL RESEARCH AT 120 DIFFERENT INSTITUTIONS. OVER 95 PERCENT OF THESE RESEARCH CONTRACTS WERE WITH UNIVERSITIES OR TEACHING HOSPITALS.

OUT OF THE WARTIME EXPERIENCES, IT WAS RECOGNIZED THAT FEDERAL SUPPORT OF RESEARCH WAS NOT ONLY APPROPRIATE AND ESSENTIAL BUT ALSO THAT IT COULD BE HIGHLY PRODUCTIVE OF BENEFIT.

DURING THE DEMOBILIZATION PERIOD, THE CRITICAL DECISION WAS MADE TO ASSIGN THE ADMINISTRATION OF ON-GOING HEALTH RESEARCH CONTRACTS TO THE NATIONAL INSTITUTES OF HEALTH. THESE TRANSFERRED CONTRACTS FORMED THE NUCLEUS OF THE EXTRAMURAL PROGRAMS OF THE NIH.

THE ORGANIZATION NOW KNOWN AS THE NIH HAD ITS BEGINNINGS IN 1887 AS A LABORATORY ON STATEN ISLAND FOR THE STUDY OF CHOLERA AND OTHER INFECTIOUS DISEASES. THE FIRST HALF CENTURY OF NIH HISTORY WAS THAT OF A VERY SMALL GOVERNMENT AGENCY CAPABLE OF ADDRESSING ONLY A FEW OF THE HEALTH PROBLEMS OF THE DAY. BUT THE POSTWAR ASSUMPTION OF ONGOING RESEARCH PROJECTS MARKED THE BEGINNING OF ITS REMARKABLE DEVELOPMENT.

BY THE MID-FIFTIES, THE OVERALL BUDGET OF THE NIH HAD GROWN TO $82 MILLION, OF WHICH MORE THAN $54 MILLION WAS EXPENDED IN GRANTS.

THEN, AS NOW, THE MAJOR INSTRUMENT USED FOR SUPPORT WAS THE RESEARCH PROJECT GRANT TO INDIVIDUAL SCIENTISTS. IT HAD BECOME A KEY PRINCIPLE THAT AWARDS SHOULD BE BASED PRIMARILY ON PEER JUDGMENT OF SCIENTIFIC MERIT. DURING THE INTERVENING YEARS, THIS REQUIREMENT HAS BEEN REPEATEDLY UPHELD AND EVEN WRITTEN INTO THE STATUTORY AUTHORITIES OF THE INSTITUTES.

BY 1955 THE TIME WAS RIPE FOR A RAPID AND MASSIVE EXPANSION OF NIH AND ITS PROGRAMS. DURING THE FOLLOWING DECADE, THE TOTAL NIH BUDGET GREW TWELVEFOLD AND EXPENDITURES FOR GRANTS FIFTEENFOLD.

THIS PERIOD OF SPECTACULAR GROWTH CAN BE VIEWED AS THE RESULT OF A FIRM ACCEPTANCE BY THE FEDERAL GOVERNMENT OF A POLICY TOWARD BIOMEDICAL RESEARCH.

THE UNDERLYING ELEMENT, OF COURSE, WAS THE ASSUMPTION BY THE FEDERAL GOVERNMENT OF A MAJOR SHARE OF THE RESPONSIBILITY FOR SUPPORT OF BIOMEDICAL RESEARCH--BASIC RESEARCH IN PARTICULAR.

A SECOND ELEMENT OF THAT POLICY, FULLY DEMONSTRATED IN THE GROWTH OF THE NIH EXTRAMURAL BUDGET, WAS THE CONTINUED HEAVY RELIANCE ON NON-FEDERAL INVESTIGATORS AND INSTITUTIONS IN CARRYING OUT THE GOVERNMENT'S PURPOSE.

(SLIDE 1 - EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET)
(SLIDE 2 - MEDICAL SCHOOLS RECEIVE 52% OF ALL AWARDS)

IT WAS FORTUNATE THAT DURING THE PERIOD OF ITS EXPLOSIVE GROWTH FROM 1955 TO THE LATE SIXTIES, THE NIH WAS DIRECTED BY AN UNUSUALLY ABLE, SENSITIVE, AND STRONG LEADER, DR. JAMES A. SHANNON.

UNDER DR. SHANNON, MANY OF THE CURRENT MECHANISMS OF SUPPORT OF BIOMEDICAL SCIENCE WERE ESTABLISHED, CONFIRMED, AND EXTENDED. THEY HAVE SERVED THE NIH AND THE SCIENTIFIC COMMUNITY WELL. JIM SHANNON INSISTED THAT THE CONGRESSIONAL MANDATES TO CONDUCT RESEARCH IN CANCER, HEART DISEASE, AND ARTHRITIS, FOR EXAMPLE, BE INTERPRETED BROADLY. HE REALIZED THAT THE SCIENCE BASE WAS NOT SUFFICIENT TO PERMIT A FRONTAL ASSAULT ON THE DISEASES THEMSELVES. HE SET ABOUT TO BUILD THE RESEARCH CAPABILITY OF THIS COUNTRY THROUGH THE INTRAMURAL PROGRAM AT BETHESDA AND THROUGH A SUBSTANTIAL EXPANSION OF THE MECHANISMS OF GRANTS-IN-AID TO INSTITUTIONS.

COROLLARY OBJECTIVES INCLUDED THE STRENGTHENING OF THE INSTITUTIONS IN WHICH BIOMEDICAL RESEARCH WOULD BE DONE AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WOULD INSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BEST AND THE BRIGHTEST YOUNG MINDS IN THE UNIVERSITIES. TOGETHER WITH HILL-BURTON MONEY FOR CLINICAL FACILITIES, NIH CONSTRUCTION FUNDS FOR RESEARCH FACILITIES MODIFIED THE TOPOGRAPHY OF THE ACADEMIC MEDICAL CENTERS AND INDIRECTLY GREATLY STRENGTHENED MEDICAL EDUCATION.

JUST THREE WEEKS AGO, DR. SHANNON'S CONTRIBUTIONS TO THE DEVELOPMENT OF THE NIH AND TO THE AMERICAN RESEARCH ENTERPRISE WERE RECOGNIZED WHEN THE HEADQUARTERS BUILDING AT BETHESDA WAS NAMED FOR HIM. IT IS HIGHLY UNUSUAL FOR A MAJOR FEDERAL BUILDING TO BE NAMED FOR A LIVING CIVIL SERVANT, BUT OUR DEBT TO HIS SCIENTIFIC STATESMANSHIP DURING A CRITICAL PERIOD IS GREAT INDEED.

IN THE INTERVENING YEARS SINCE 1968, THE NIH HAS CONTINUED TO GROW--BUT, OF COURSE, IT WOULD HAVE BEEN UNREALISTIC TO EXPECT THE RATE OF GROWTH TO MATCH THAT OF EARLIER YEARS.

IN 1975 THE APPROPRIATION FOR THE NIH EXCEEDED $3 BILLION FOR THE FIRST TIME. BUT IN THE PAST DECADE, THE GROWTH IN SUPPORT HAS BEEN MORE APPARENT THAN REAL--THE 1979 APPROPRIATION OF $3.2 BILLION REPRESENTS AN ALL-TIME HIGH IN CONSTANT DOLLARS, BUT WAS WORTH ONLY $1.92 BILLION IN 1972 DOLLARS. SINCE 1979 AND BETWEEN 1979 and 1982, THE CONSTANT DOLLAR LEVEL FELL BY 12 PERCENT. A SLIGHT INCREASE TO THE 1983 LEVEL OF $1.77 BILLION INDICATES THAT FOR THE PRESENT AT LEAST THE DECLINE IN PURCHASING POWER HAS LEVELED OFF. BETWEEN 1972 AND 1982, AN INCREASE OF ABOUT 15 PERCENT WAS ALMOST EXACTLY MATCHED BY THE INCREASE IN INDIRECT COSTS. THEREFORE, THE DOLLARS AVAILABLE FOR RESEARCH HAVE BEEN ESSENTIALLY CONSTANT FOR A DECADE, AT A TIME WHEN THE NUMBER OF CAPABLE AND MATURING SCIENTISTS HAS MUCH INCREASED AND SCIENTIFIC OPPORTUNITY IS GREATER THAN EVER BEFORE. CLEARLY, ALL OF US AT NIH, MYSELF INCLUDED, WOULD PREFER JIM SHANNON's PROBLEMS TO THOSE OF 1983.

(SLIDE 3 - TOTAL NIH APPROPRIATIONS 1972-82)
(SLIDE 4 - TRENDS IN EXTRAMURAL AWARDS 1972-82)

LAST MONDAY, PRESIDENT REAGAN PRESENTED HIS BUDGET REQUEST FOR 1984. AS YOU KNOW, IT REFLECTS THE GENERAL CONCERN OVER THE SIZE OF THE DEFICIT AND CALLS FOR REDUCTIONS IN THE AMOUNTS ALLOCATED TO MANY SO-CALLED "CONTROLLABLE" PROGRAMS. BIOMEDICAL RESEARCH IS SUCH A PROGRAM. THE 1984 REQUEST FOR NIH IS $4.077 BILLION--AN INCREASE OF $73 MILLION OR 1.8 PERCENT OVER THE CURRENT LEVEL. IN THE ABSENCE OF INTERNAL ADJUSTMENTS, THE REQUESTED BUDGET WOULD PERMIT NIH TO SUPPORT ONLY AN ESTIMATED 3,676 NEW AND COMPETING PROJECT GRANTS AS COMPARED WITH THE ESTIMATED 1983 LEVEL OF 4,914. WITH THE INCLUSION OF NONCOMPETING AWARDS, THE TOTAL NUMBER OF RESEARCH PROJECT GRANTS WOULD BE 15,236. HOWEVER, WE CURRENTLY EXPECT TO FUND 4,105 NEW AND COMPETING GRANTS AND 15,665 ALTOGETHER, FOLLOWING SOME INTERNAL RE-BUDGETING; AND NEGOTIATIONS WITH OMB ARE CONTINUING.

THUS, MY DISCUSSION OF THE "ZERO-SUM GAME" IS PARTICULARLY TIMELY, FOR IT IS INDEED A LIVE ISSUE FOR ALL OF US AT THIS TIME.

FOR PERSPECTIVE, HOWEVER, I THINK I SHOULD OBSERVE THAT AS COMPARED WITH MANY OTHER "CONTROLLABLE" FEDERAL PROGRAMS, BIOMEDICAL RESEARCH HAS FARED RELATIVELY WELL OVER THE PAST FEW YEARS. IT WOULD BE REMISS OF ME NOT TO MENTION THE IMPORTANT ROLE PLAYED BY TWO MEN WHO HAVE TIRELESSLY CHAMPIONED THE CAUSE OF NIH WITHIN THE ADMINISTRATION. ONE OF THEM IS FORMER SECRETARY RICHARD S. SCHWEIKER, WHOSE LAST DAY IN OFFICE WAS FEBRUARY 2, AND THE OTHER IS YOUR FELLOW TEXAN, ASSISTANT SECRETARY FOR HEALTH, ED BRANDT.

ALTHOUGH IN RETROSPECT A PROGRESSIVE SHIFT OF NIH DOLLARS AMONG FUNDING INSTRUMENTS BEGAN IN ABOUT 1974 WHEN THE NIH BUDGET BEGAN TO LEVEL OFF, THE

FIRST SUBSTANTIAL DECLINE IN CONSTANT DOLLAR BUDGETS IN 1980 SIGNALLED THAT THE TIME HAD COME FOR A REASSESSMENT OF PROGRAMS AND POLICIES IN ORDER TO MAINTAIN THE MOMENTUM OF SCIENTIFIC INQUIRY IN THE FACE OF LIMITED RESOURCES.

THE ANSWER WAS AN ARTICULATED POLICY OF "STABILIZATION," WHICH FORMALIZED AS AN OBJECTIVE SEVERAL TRENDS ALREADY UNDERWAY. UNDER THIS POLICY, NIH SET AS MINIMAL GOALS THE FUNDING OF 5,000 NEW AND COMPETING GRANTS AND 10,000 TRAINEES AND FELLOWS PER YEAR.

OUR PRIMARY CHALLENGE IS: HOW BEST TO CAPITALIZE ON THE VAST SCIENTIFIC OPPORTUNITY BEFORE US DURING THE TIME OF CONSTRAINED RESOURCES? THE BUDGET FOR BIOMEDICAL RESEARCH, MORE SPECIFICALLY THAT OF THE NIH, CANNOT BE EXPECTED TO GROW SUBSTANTIALLY IN THE IMMEDIATE FUTURE. BUT IT IS A VERY LARGE BUDGET--MORE THAN $4 BILLION IN THE CURRENT FISCAL YEAR. IT IS A BUDGET THAT CONFIRMS THE SUPPORT OF CONGRESS AND THE ADMINISTRATION FOR BIOMEDICAL RESEARCH. BUT WE ARE IN A BUDGETARY STEADY STATE AND ARE LIKELY TO BE SO UNTIL THERE IS SUBSTANTIAL IMPROVEMENT IN THE ECONOMY.

SEVERAL ADJUSTMENTS WILL BE NECESSARY IF WE ARE TO SECURE THE GREATEST AMOUNT OF THE BEST SCIENCE WITHIN AVAILABLE RESOURCES. THIS ZERO-SUM GAME WILL HAVE TO BE PLAYED WITH UNUSUAL SKILL IF WE ARE TO AVOID A STIFLING OF INITIATIVE AND LOSS OF MOMENTUM AT A TIME WHEN SCIENTIFIC OPPORTUNITY SEEMS BRIGHTER THAN EVER BEFORE.

PROGRAMS, POLICIES, AND PRIORITIES OF THE NIH HAVE BEEN MODIFIED AND EXPANDED THROUGH THE YEARS, BUT THE FUNDAMENTAL MISSION AND PRINCIPLES OF THE AGENCY HAVE NOT CHANGED DURING ITS MODERN ERA.

IN CARRYING OUT THAT MISSION, CERTAIN PRINCIPLES HAVE EVOLVED THAT MUST CONTINUE TO GUIDE OUR DECISIONS.

ONE PRINCIPLE IS THAT THE PURSUIT OF BASIC KNOWLEDGE IS THE FOUNDATION OF ALL PROGRESS IN THE HEALTH SCIENCES. ANY RELAXATION OF THAT NECESSARILY LONG-TERM OBJECTIVE IN FAVOR OF SHORT-TERM ADVANTAGE IS A THREAT TO EVENTUAL SUCCESS AGAINST DISEASE AND SUFFERING.

A SECOND FUNDAMENTAL PRINCIPLE IS THAT INVESTIGATOR-INITIATED RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY. THROUGH COMPETING RESEARCH PROJECTS, WE TAP THE BEST MINDS AND MOST CREATIVE IDEAS, WEIGH THEM THROUGH PEER REVIEW OF SUBSTANCE AND METHODOLOGY, AND TEST THEM THROUGH CHALLENGE AND OPEN EXCHANGE OF INFORMATION.

A THIRD ELEMENT IN THESE TIME-TESTED PRINCIPLES IS THAT THERE IS A NEED TO ASSURE A CONTINUING SUPPLY OF WELL-TRAINED SCIENTISTS TO MEET NATIONAL HEALTH GOALS.

A FOURTH PRINCIPLE IS THAT THE PRIMARY MEANS FOR PURSUIT OF BASIC RESEARCH IS PROVIDED BY THE ACADEMIC COMMUNITY, THAT BEING WHERE THE MAJORITY OF SCIENTISTS ARE TO BE FOUND.

A FINAL PRINCIPLE IS THAT OF PUBLIC ACCOUNTABILITY--BY THE GOVERNMENT AGENCIES AND BY THE RECIPIENTS OF GOVERNMENT SUPPORT. WE MUST FIRST ASSURE THAT PUBLIC FUNDS ARE APPROPRIATELY USED FOR PUBLIC PURPOSES. THOSE WHO RECEIVE NIH SUPPORT MUST CONDUCT THEIR WORK IN ACCORD WITH SCIENTIFIC RIGOR AND MAKE CERTAIN THAT THE HIGHEST ETHICAL STANDARDS ARE OBSERVED. IT IS ALSO OUR RESPONSIBILITY TO SEE THAT NEW KNOWLEDGE IS BROUGHT INTO MEDICAL PRACTICE AS RAPIDLY AS APPROPRIATE.

WE MUST ADHERE TO THOSE PRINCIPLES AS WE ESTABLISH PRIORITIES AND POLICIES TO CARRY OUT THE MISSION OF THE NIH--AS WE DEAL WITH CURRENT REALITIES--GREAT SCIENTIFIC OPPORTUNITY AND CONSTRAINED RESOURCES. IN THAT CONTEXT, WE HAVE PLACED THE HIGHEST PRIORITY ON THE FOLLOWING OBJECTIVES:

(1) TO STABILIZE THE INVESTIGATOR-INITIATED BIOMEDICAL RESEARCH PROJECT BASE;

(2) TO SUPPORT THE TRAINING OF THE OPTIMUM NUMBER OF NEW INVESTIGATORS TO ASSURE CONTINUITY OF HIGH QUALITY RESEARCH IN THE FUTURE;

(3) TO ORGANIZE THE AGENCY FOR MAXIMUM EFFICIENCY IN SUPPORT OF MODERN BIOMEDICAL RESEARCH; AND

(4) TO SUPPORT HIGH QUALITY CLINICAL TRIALS TO ASSESS THE EFFICACY OF NEWLY DISCOVERED THERAPIES, DRUGS, AND DEVICES.

IN TERMS OF SETTING OUR PRIORITIES, I CONSIDER THE PRIMARY ISSUE TO BE THAT OF STABILIZATION. THE STABILIZATION POLICY MAKES A POWERFUL STATEMENT TO THE EXTRAMURAL COMMUNITY. IT SAYS THAT NIH IS DOING ITS UTMOST CONSISTENT WITH PROGRAM BALANCE AND CONGRESSIONAL MANDATES AND DIRECTIVES TO ASSURE THAT THE BEST RESEARCH WILL BE ADEQUATELY FUNDED, THAT YOUNG SCIENTISTS WILL HAVE OPPORTUNITIES IN RESEARCH, AND THAT WE WILL PROTECT THEIR ENTRY INTO THE RESEARCH ENTERPRISE--NOT OUT OF CHARITY OR AS AN EMPLOYMENT PROGRAM FOR SCIENTISTS--BUT BECAUSE THE VITALITY AND SUCCESS OF THE RESEARCH ENDEAVOR DEPENDS ON THEM.

ABOUT 50 PERCENT OF ALL AWARDS IN RECENT YEARS FOR NEW TRADITIONAL RESEARCH PROJECTS (R01) ARE MADE TO SCIENTISTS WHO HAVE NEVER BEFORE BEEN PRINCIPAL INVESTIGATORS. THUS, OVER 1900 OR ABOUT 12 PERCENT OF OUR TOTAL PORTFOLIO OF SOME 16,000 GRANTS ARE IN THE HANDS OF SCIENTISTS IN THEIR FIRST TERM AS PRINCIPAL INVESTIGATORS.

UNDER THE STABILIZATION POLICY, INVESTIGATOR-INITIATED RESEARCH PROJECTS AND RESEARCH TRAINING HAVE BEEN GIVEN TOP PRIORITY. THE CONGRESS HAS INDICATED ITS HEARTY ACCORD WITH THIS PRIORITY.

BUT THE STABILIZATION POLICY ALSO HAS ITS DOWN SIDE. IN ORDER TO FUND 5,000 NEW AND COMPETING PROJECTS, DOLLARS HAVE BEEN SHIFTED FROM OTHER MECHANISMS EACH YEAR SINCE 1974 (SLIDE 5). WHILE THE PROPORTION OF THE NIH BUDGET ASSIGNED TO SUPPORT INVESTIGATOR-INITIATED RESEARCH PROJECTS HAS GROWN, OTHER MECHANISMS HAVE BEEN CURTAILED, ESPECIALLY NIH INITIATIVES TO EMPHASIZE SPECIAL AREAS OR ACTIVITIES AS IN CENTERS, OR TO ANSWER SPECIFIC QUESTIONS AS IN CLINICAL TRIALS PURSUED THROUGH CONTRACTS.

AFTER SEVERAL TURNS OF THE RATCHET, MANY INSTITUTE DIRECTORS FEEL THAT FURTHER SHIFTS WOULD SERIOUSLY LIMIT THEIR ABILITY TO MEET OTHER PROGRAM GOALS AND TO MAINTAIN PROGRAM BALANCE. IF THE RATE OF INCREASE IN PERCENT OF THE NIH BUDGET DEVOTED TO THE EXTRAMURAL GRANT COMPONENT WERE TO CONTINUE, IT WOULD REACH 100 PERCENT IN 1993!

(SLIDE 5 ALLOCATION OF EXTRAMURAL AWARDS)

(SLIDE 6 AVERAGE RESEARCH PROJECT GRANT)

TWO IMPORTANT FACTORS IN THIS SITUATION ARE THAT THE AVERAGE COST PER GRANT HAS GROWN FASTER THAN THE RATE OF INFLATION, AND INDIRECT RESEARCH PROJECT COSTS HAVE INCREASED FASTER THAN DIRECT COSTS. THE QUESTION THEN IS HOW TO ENSURE THAT ALL ESSENTIAL AND VITAL ACTIVITIES ARE CONTINUED WHILE STABILITY IN THE RESEARCH AND TRAINING BASE IS MAINTAINED.

AT THE SAME TIME, WE MUST ADDRESS MORE AGGRESSIVELY THE RESEARCH RESOURCES THAT MAINTAIN THE QUALITY OF THE ENVIRONMENT IN WHICH MODERN BIOMEDICAL RESEARCH IS PERFORMED. WE WILL CONTINUE TO FUND SHARED PROGRAMS. BUT WE NEED TO DO MORE TO RESTORE THE NATION's INSTRUMENTATION BASE AND TO MODERNIZE THE LABORATORIES NEEDED TO CONDUCT BIOMEDICAL RESEARCH.

AT THE HEART OF ALL THESE CONSIDERATIONS IS THE NEED TO STRETCH THE RESEARCH DOLLAR WITHOUT COMPROMISING THE QUALITY OF INVESTIGATION. OUR EMPHASIS ON QUALITY RATHER THAN ON DISTRIBUTION HAS CREATED SOME ANXIETY IN THE RESEARCH COMMUNITY AND HAS PROMPTED VARIED RESPONSES.

DURING 1982, ALTHOUGH WE FUNDED 5,027 NEW AND COMPETING RESEARCH AWARDS, THIS FIGURE REPRESENTS ONLY ABOUT A THIRD OF APPROVED GRANT APPLICATIONS.

(SLIDE 7 COUNCIL RECOMMENDED FOR APPROVAL AND AWARD RATES)

WHILE WE SHARE A DEEP CONCERN FOR SCIENTISTS WHOSE DESERVING PROJECTS WE CANNOT FUND, WE FEEL THAT THE INTERESTS OF SCIENCE ARE BEST SERVED BY FUNDING THE MOST MERITORIOUS WORK AS JUDGED BY THE PEER REVIEW SYSTEM AND BY ASSURING THAT SUCH PROJECTS ARE FUNDED PRUDENTLY YET ADEQUATELY FOR THE EXECUTION OF THE STUDY.

IN THE SEARCH FOR WAYS TO FUND GREATER NUMBERS OF PROJECTS, SOME HAVE SUGGESTED A LIMITATION OF THE DOLLAR SUPPORT AWARDED TO ANY INDIVIDUAL PRINCIPAL INVESTIGATOR. THIS PROPOSAL HAS TAKEN SEVERAL FORMS. ONE WOULD LIMIT THE NUMBER OF DOLLARS PER PROJECT OR PER LABORATORY. ANOTHER WOULD BE TO LIMIT THE NUMBER OF GRANTS IN THE NAME OF ANY PRINCIPAL INVESTIGATOR. AT PRESENT, ABOUT 10 PERCENT OF PRINCIPAL INVESTIGATORS HAVE TWO OR MORE TRADITIONAL RESEARCH PROJECT GRANTS.

A THIRD PROPOSED MECHANISM IS THAT OF A SLIDING SCALE IN THE PAYMENT OF APPROVED AWARDS. IT IS SUGGESTED THAT NIH SHOULD FUND GRANTS OF THE VERY HIGHEST PRIORITY SCORES AT 100 PERCENT OF THE AWARD RATE; THE NEXT CATEGORY OF PRIORITY SCORES AT 90 PERCENT, FOLLOWED BY 80 PERCENT, AND SO ON. WE HAVE EXAMINED THIS CONCEPT VERY CAREFULLY BUT FIND IT FLAWED IN SEVERAL PARTICULARS. AS WE HAVE REVIEWED ALTERNATIVES FOR SPREADING RESEARCH DOLLARS ACROSS A LARGE NUMBER OF INVESTIGATORS, WE HAVE FOUND OURSELVES REAFFIRMING THE TRADITIONAL PRACTICE OF AWARDING GRANTS ON THE DUAL BASIS OF SCIENTIFIC MERIT AND PROGRAM RELEVANCE AS DETERMINED BY STUDY SECTION AND COUNCIL REVIEW.

INTIMATELY RELATED TO THESE EFFORTS TO STRETCH THE GRANT DOLLAR ARE ISSUES THAT APPLY TO THE VERY NATURE OF THE EXTREMELY PRODUCTIVE PARTNERSHIP THAT HAS BEEN DEVELOPED BETWEEN THE FEDERAL GOVERNMENT AND ACADEMIA. THE RELATIONSHIP HAS BEEN TESTED MANY TIMES AND PROBLEMS HAVE BEEN SOLVED THROUGH OPEN AND CANDID DISCUSSION. IN THE CONFIDENCE THAT WE CAN OVERCOME TODAY'S PROBLEMS BY

FOLLOWING THE SAME COURSE, WE HAVE OPENED SUCH SENSITIVE SUBJECTS AS INDIRECT COST REIMBURSEMENT AND SALARY SUPPORT.

LET ME DISCUSS BRIEFLY THE PROBLEM OF INDIRECT COSTS AS SEEN BY THE NIH.

PRIOR TO 1966, THE NIH PAID A FLAT RATE OF 8 PERCENT, THEN 15 PERCENT, AND FINALLY 20 PERCENT OF THE TOTAL AWARD TO COVER THE INDIRECT COSTS OF A RESEARCH GRANT. A MAJOR STUDY IN 1967 RECOMMENDED THAT NIH ABANDON THE FLAT RATE AND, INSTEAD, PAY A NEGOTIATED RATE BASED ON AUDITS. FOR THE NEXT SIX YEARS, THE AVERAGE INDIRECT COST RATE ROSE RAPIDLY--BY 1972 REACHING 21 PERCENT. SINCE THAT TIME, IT HAS RISEN LESS SHARPLY BUT AT A STEADY RATE, REACHING 30 PERCENT BY FISCAL YEAR 1982. PUT ANOTHER WAY, FOR EACH DOLLAR OF DIRECT COSTS, AN ADDITIONAL 43 CENTS GO FOR INDIRECT COSTS.

(SLIDE 8 INDIRECT COST PERCENTAGE)

UNIVERSITY ADMINISTRATORS, UNDERSTANDABLY, ARE CONCERNED ABOUT ANY MODIFICATION OF OUR APPROACH TO INDIRECT COSTS AND EMPHASIZE THAT INDIRECT COSTS ARE TRUE COSTS OF RESEARCH, A POINT WE DO NOT CONTEST. CONGRESS IS CONCERNED ABOUT THE RATE OF GROWTH OF INDIRECT COSTS BUT HAS PROVIDED ADDITIONAL FUNDS FOR THE CURRENT YEAR FOR THE FULL PAYMENT OF SUCH COSTS.

AT ISSUE ARE THE CONTAINMENT OF INDIRECT COSTS AND THE EXTENT OF COST SHARING BETWEEN THE UNIVERSITIES AND THE FEDERAL GOVERNMENT. THIS HAS BECOME A DIVISIVE ISSUE WHICH REQUIRES EARLY RESOLUTION.

ANOTHER ISSUE THAT WE ARE CURRENTLY EXAMINING IS THE TREND IN THE SALARY SUPPORT OF PRINCIPAL AND OTHER INVESTIGATORS AS A PERCENTAGE OF THE RESEARCH AWARD. WE RECOGNIZE THAT THIS IS A COMPLEX AND SENSITIVE ISSUE BUT ONE THAT REQUIRES ASSESSMENT.

BUT AS WE SEEK REASONABLE AND EQUITABLE WAYS FOR STRETCHING THE RESEARCH DOLLAR, WE MUST NEVER LOSE SIGHT OF THE FACT THAT TRAINING IS AN INTEGRAL PART OF THE NIH MISSION. THE TRAINING OF THE NEXT GENERATION OF SCIENTIFIC INVESTIGATORS IS ESSENTIAL TO THE CONTINUED VIGOR OF SCIENTIFIC INQUIRY. NIH HAS SOUGHT TO PROVIDE STABLE SUPPORT FOR RESEARCH TRAINING PROGRAMS. SOME 10,700 TRAINEE POSITIONS WERE SUPPORTED IN 1981 AND 10,400 LAST YEAR. THIS YEAR WE EXPECT TO SUPPORT ALMOST 10,000 TRAINEE POSITIONS. WE ARE WORKING CLOSELY WITH THE NATIONAL ACADEMY OF SCIENCES TO IDENTIFY NEEDS AND MATCH THEM WITH OPPORTUNITIES IN SCIENCE.

ONE SUBJECT OF SPECIAL CONCERN IS THE PRESENT AND FUTURE STATE OF CLINICAL RESEARCH. A BURGEONING OF FUNDAMENTAL KNOWLEDGE IN THE PAST DECADE HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH. NEVERTHELESS, A DIMINISHING

PERCENTAGE OF PHYSICIANS HAVE INTEREST IN APPLYING THEMSELVES TO THE CLINICAL RESEARCH NEEDS OF TOMORROW. SOME QUANTITATIVE DATA MAY SERVE TO EMPHASIZE THE SITUATION. THERE WAS A DECLINE IN THE NUMBER OF PHYSICIANS HOLDING RESEARCH PROJECT AWARDS FROM ABOUT 3400 IN 1968 TO ABOUT 2500 IN 1973. SINCE THAT TIME, THE NUMBER HAS INCREASED SLIGHTLY, BUT IN 1981 IT WAS STILL BELOW 3000. THE PERCENTAGE OF GRANTS HELD BY M.D. PRINCIPAL INVESTIGATORS DROPPED FROM ABOUT 35 PERCENT OF ALL RESEARCH GRANT AWARDS IN 1968 TO ABOUT 23 PERCENT IN 1981. DURING THE SAME TIME, THE PERCENTAGE OF GRANTS HELD BY PH.D. PRINCIPAL INVESTIGATORS INCREASED FROM 52 TO 67 PERCENT. THE PROPORTION HELD BY M.D.-PH.D. PRINCIPAL INVESTIGATORS HAS REMAINED NEARLY STEADY AT ABOUT 10 PERCENT OF THE TOTAL.

(SLIDE 9 P.I.'s HOLDING MD, PhD DEGREES)

IN MY VIEW, THE TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT. SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MEDICAL SCIENCE.

WE ARE ALWAYS CONSIDERING APPROACHES AND INITIATIVES TO ENCOURAGE M.D.s TO ENTER INTO OR REMAIN IN RESEARCH CAREERS AND TO IMPROVE THEIR EFFECTIVENESS. FOR EXAMPLE, AT THE UNDERGRADUATE MEDICAL STUDENT LEVEL, WE CONTINUE TO GIVE THE MEDICAL SCIENTIST TRAINING PROGRAM TOP PRIORITY IN OUR TRAINING PORTFOLIO. THE NATIONAL RESEARCH SERVICE AWARDS PROGRAM ALSO PERMITS SHORT-TERM TRAINING OF MEDICAL STUDENTS. AND I SHOULD POINT OUT THAT THE NIH INTRAMURAL RESEARCH PROGRAM PROVIDES TRAINING FOR MANY CLINICAL INVESTIGATORS.

THIS GROWING PROBLEM HAS ALSO RECEIVED CONSIDERABLE ATTENTION IN THE CONGRESS. LAST FALL, FOR EXAMPLE, THE REPORT OF THE HOUSE COMMITTEE ON APPROPRIATIONS NOTED THAT YOUNG PHYSICIANS ARE OFTEN DISSUADED FROM APPLYING FOR RESEARCH TRAINING BECAUSE THEY PERCEIVE INSTABILITY IN THE FEDERAL COMMITMENT TO RESEARCH AND BECAUSE OF THEIR AWARENESS THAT A RESEARCH CAREER REPRESENTS A SUBSTANTIAL FINANCIAL SACRIFICE WHEN COMPARED WITH ALMOST ANY OTHER FORM OF MEDICAL PRACTICE.

(SLIDE 10 PERCENTAGE OF NIH POSTDOCTORAL TRAINEES BY DEGREE)

CERTAINLY THE INCREASED LENGTH OF TRAINING REQUIRED AND THE ADDITIONAL DEBT LOAD INCURRED BY THE PHYSICIAN ARE BARRIERS. ADD TO THAT THE FACT THAT THE

RESEARCH TRAINING STIPEND AVERAGES SOME $4500 LESS THAN AN EQUIVALENT HOUSE STAFF POSITION IN A HOSPITAL. AN INCREASE IN THE PHYSICIAN'S STIPEND MIGHT ATTRACT M.D.s INTO RESEARCH TRAINING, BUT GIVEN A LIMITED BUDGET, THIS WOULD FORCE A REDUCTION IN THE NUMBER OF TRAINEES.

IF WE ARE TO DEAL EFFECTIVELY WITH THE COMPLEX CHALLENGES OF THE MODERN SCIENTIFIC ENTERPRISE, WE MUST ALSO GIVE ATTENTION TO THE ADMINISTRATIVE STRUCTURE THAT SERVES IT. OF ALL AREAS OF HUMAN ENDEAVOR, THE MANAGEMENT OF SCIENCE IS ONE OF THE MOST VULNERABLE TO RIGIDITY.

AS THE KNOWLEDGE BASE INCREASES, AND THERE IS WIDER RECOGNITION OF THE POTENTIAL FOR SUCCESSFUL INTERVENTION IN DISEASE PROCESSES, PRESSURE FOR ADDITIONAL, NARROWLY FOCUSED RESEARCH EFFORTS CAN BE EXPECTED. IN LOOKING BACK AT THE DEVELOPMENT OF THE FEDERAL BIOMEDICAL RESEARCH ENTERPRISE, HOWEVER, IT IS CLEAR THAT THE IMPETUS FOR ITS GROWTH OFTEN CAME FROM JUST SUCH PRESSURES.

THE NAMES OF THE CONSTITUENT INSTITUTES OF THE NIH STAND AS ELOQUENT PROOF OF THE POWER OF PUBLIC CONCERN ABOUT SPECIFIC DISEASES AND FAMILIES OF DISORDERS.

BUT TODAY BIOMEDICAL SCIENCE FOCUSES INCREASINGLY ON FUNDAMENTAL PROCESSES OF LIFE AND INTERRELATIONSHIPS AMONG DISEASE ENTITIES. IN MY VIEW, CREATION OF ADDITIONAL CATEGORICAL DISEASE-SPECIFIC INSTITUTES AT NIH IS NOT THE MOST EFFICIENT WAY TO ADMINISTER RESEARCH. YET THE PRESSURES OF SPECIAL INTEREST GROUPS FOR SUCH APPROACHES HAS MARKEDLY INCREASED IN THE PAST FEW YEARS AS RESEARCH SUPPORT HAS BECOME MORE COMPETITIVE.

THE QUESTION IS: HOW CAN NIH BEST SUPPORT AND MANAGE THE CONTINUING EVOLUTION OF THE HEALTH SCIENCES FOR MAXIMUM PUBLIC BENEFIT? WE HAVE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN 18-MONTH STUDY OF THE ORGANIZATION OF NIH. THE STUDY WILL EXAMINE THE ADEQUACY AND EFFICIENCY OF THE PRESENT STRUCTURE AND DEVELOP A SET OF CRITERIA BY WHICH WE CAN WEIGH AND DETERMINE THE NEED FOR CHANGE.

IN THE COMING YEAR, OUR ADMINISTRATIVE INGENUITY AND FLEXIBILITY WILL ALSO BE TESTED IN OUR RESPONSE TO THE NEED FOR CLINICAL TRIALS. CLINICAL TRIALS ARE THE FINAL STEP IN THE TESTING AND VALIDATION OF MEDICAL INTERVENTIONS AND IDEALLY SHOULD BE PERFORMED ON EACH NEW PREVENTIVE OR THERAPEUTIC MODALITY BEFORE ITS INTRODUCTION INTO CLINICAL PRACTICE. A SCIENTIFICALLY RIGOROUS TRIAL, HOWEVER, IS SO COSTLY IN FUNDS AND PERSONNEL AND IS SO TIME-CONSUMING THAT THIS IDEAL CANNOT BE REALIZED FOR EACH MEDICAL INNOVATION. CONSEQUENTLY, TRIALS ARE MOUNTED ONLY FOR MEDICAL INTERVENTION OF THE GREATEST IMPORTANCE AND POTENTIALLY WIDEST APPLICABILITY.

IN RESPONSE TO THIS PROBLEM, NIH IS SEEKING GREATER COLLABORATION WITH PRIVATE INDUSTRY IN THE SUPPORT AND CONDUCT OF CLINICAL TRIALS AND IS EXPLORING ALTERNATIVE OR COMPLEMENTARY APPROACHES TO THE COLLECTION OF DATA TRADITIONALLY GATHERED THROUGH PROSPECTIVE CLINICAL TRIALS. WE MUST ALSO ESTABLISH BETTER CRITERIA FOR SELECTION OF THE TRIALS TO BE SUPPORTED. AT PRESENT TOO MANY LARGE, LENGTHY AND EXPENSIVE TRIALS END UP INCONCLUSIVELY.

THESE CONSIDERATIONS OF CLINICAL TRIALS HAVE BROUGHT INTO SOMEWHAT SHARPER FOCUS A POLICY QUESTION THAT HAS NOT IN THE PAST RECEIVED SUSTAINED ATTENTION. HOW CAN THE FEDERAL GOVERNMENT, ACADEMIA, AND INDUSTRY COLLABORATE MOST EFFECTIVELY IN THE BIOMEDICAL RESEARCH ENTERPRISE?

EACH PARTNER IN SUCH A THREE-WAY ARRANGEMENT HAS INTERESTS AT STAKE THAT CANNOT BE SACRIFICED. YET THERE ARE MANY COMMON INTERESTS AS WELL. EACH OF US IS CHALLENGED TO FIND WAYS FOR MAKING OPTIMUM JOINT USE OF THE UNIQUE RESOURCES WE CAN OFFER TO SUCH PARTNERSHIP.

* * *

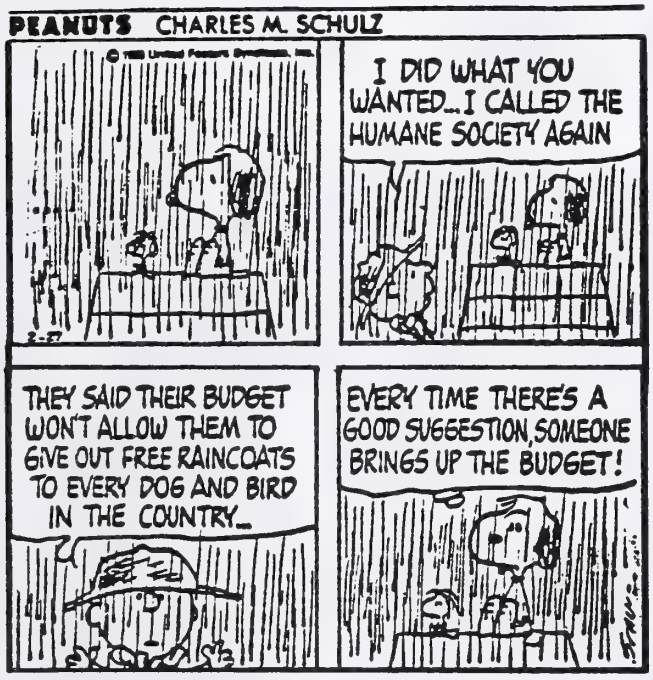
I HAVE TRACED IN SOME DETAIL THE PHENOMENAL GROWTH OF THE PRINCIPAL BIOMEDICAL RESEARCH ARM OF THE FEDERAL GOVERNMENT AND THE CONCOMITANT EXPANSION OF THE BIOSCIENCES IN THE NATION'S ACADEMIC COMMUNITY. TOGETHER WE HAVE WAGED A VERY SUCCESSFUL CAMPAIGN AGAINST DISEASE AND SUFFERING—AND THERE IS EVERY EXPECTATION THAT EVEN MORE DRAMATIC SUCCESSES LIE JUST AHEAD.

FOR MOST OF THE PAST 30 YEARS, WE HAVE HAD AMPLE RESOURCES TO DEPLOY WHATEVER FORCES WERE NEEDED TO CAPITALIZE ON BREAKTHROUGH AREAS WITHOUT WEAKENING THE SLOW AND STEADY PROGRESS ACROSS THE ENTIRE FRONT LINE. OUR ADAPTATION TO NEW OPPORTUNITIES IN THE PAST HAS TAKEN THE FORM OF GENERAL GROWTH.

NOW, WITH ECONOMIC CONSTRAINTS ON THE SIZE OF THE TOTAL SYSTEM, WE WILL NEED TO REDEPLOY RESOURCES FROM ONE AREA TO ANOTHER TO ADJUST PRIORITIES THAT AFFECT BOTH RESEARCH AND TRAINING IN RESPONSE TO FISCAL REALITIES.

THE ZERO-SUM GAME IS NEW TO THIS GENERATION OF BIO-SCIENTISTS. OUR EXPERIENCE HAS BEEN ADAPTATION TO GENERAL EXPANSION. OUR CHALLENGE IS ADAPTATION TO A STEADY-STATE. IT IS IMPERATIVE THAT WITHIN THE NIH, THE ADMINISTRATION, THE CONGRESS, AND THE ACADEMIC COMMUNITY, THE NECESSARY WISDOM AND ADAPTABILITY BE EXERCISED TO MEET THE NEW CONDITION WITHOUT SACRIFICE OF SCIENTIFIC QUALITY.

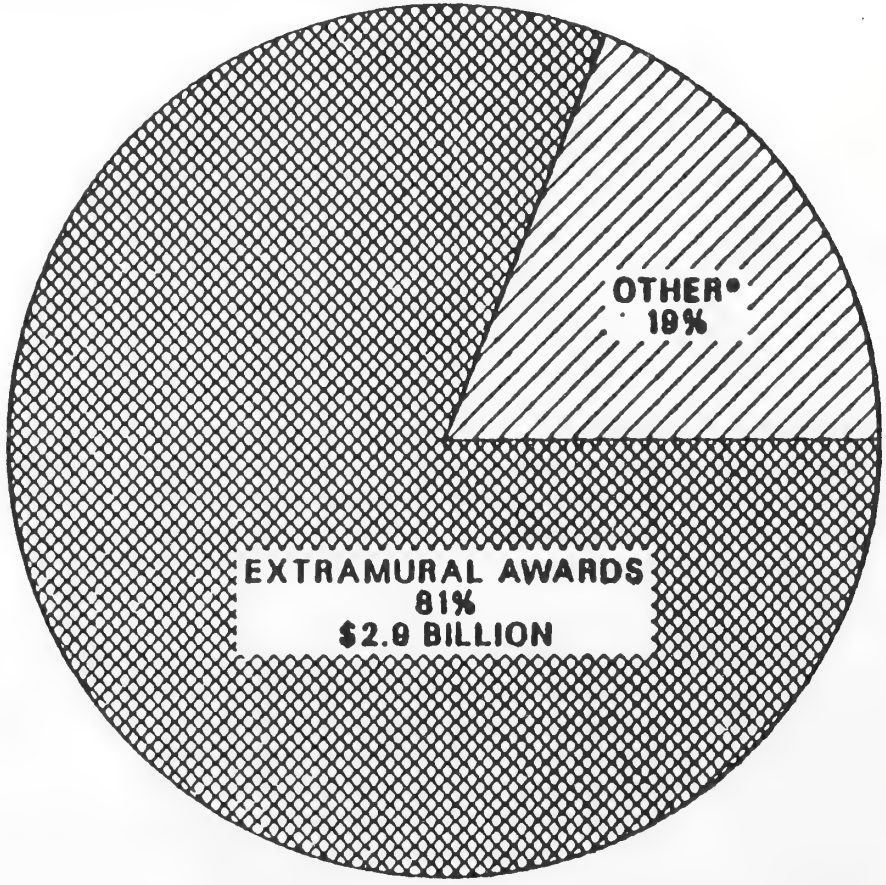
ALL OF THIS LENGTHY DISCUSSION IS CAPTURED BY A RECENT PEANUTS CARTOON:


PEANUTS CHARLES M. SCHULZ
I DID WHAT YOU WANTED... I CALLED THE HUMANE SOCIETY AGAIN
THEY SAID THEIR BUDGET WON'T ALLOW THEM TO GIVE OUT FREE RAINCOATS TO EVERY DOG AND BIRD IN THE COUNTRY...
EVERY TIME THERE'S A GOOD SUGGESTION, SOMEONE BRINGS UP THE BUDGET!

(1)

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET

FISCAL YEAR 1982



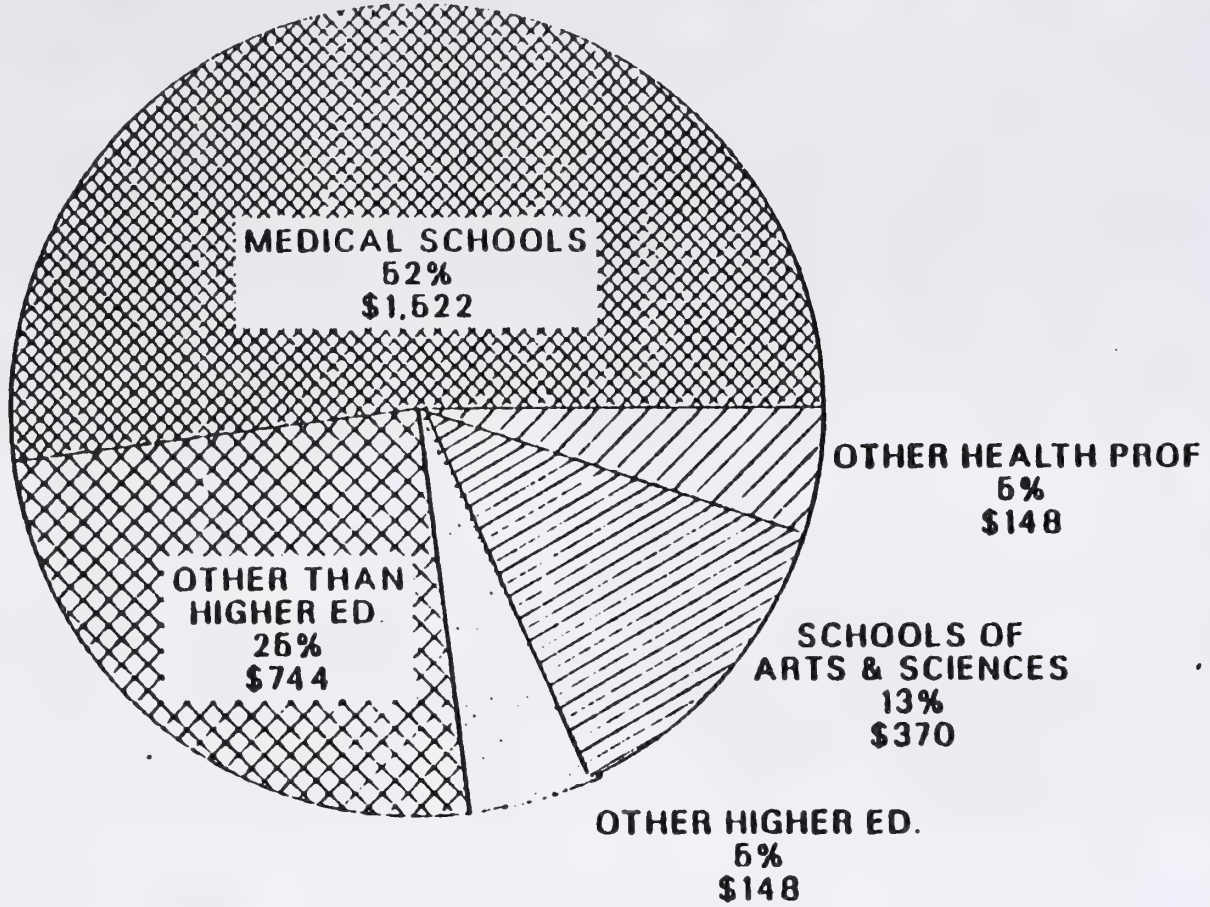
TOTAL - $3.6 BILLION

*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

Extramural
Funds

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



FY 1982*

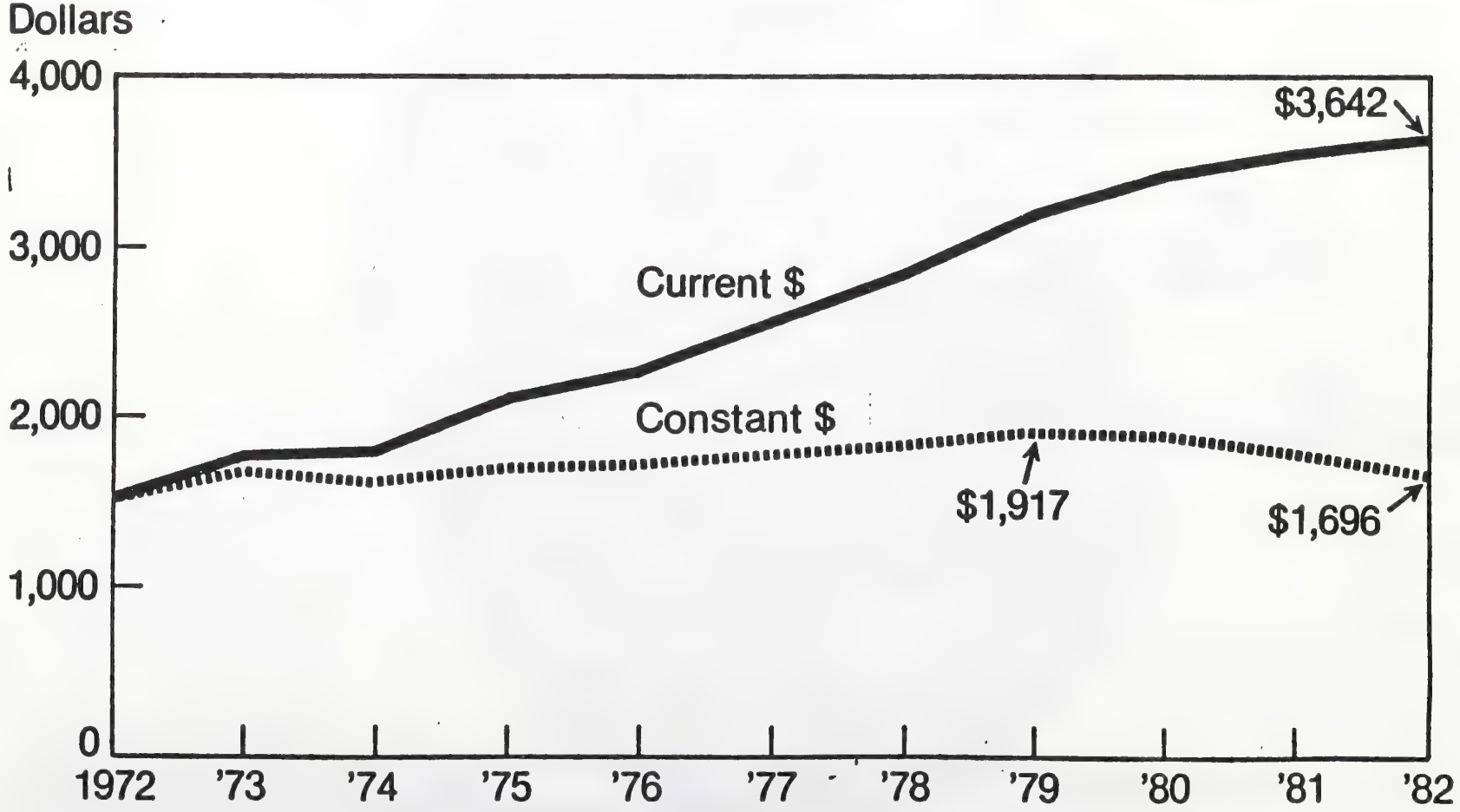
$2,933 MILLION

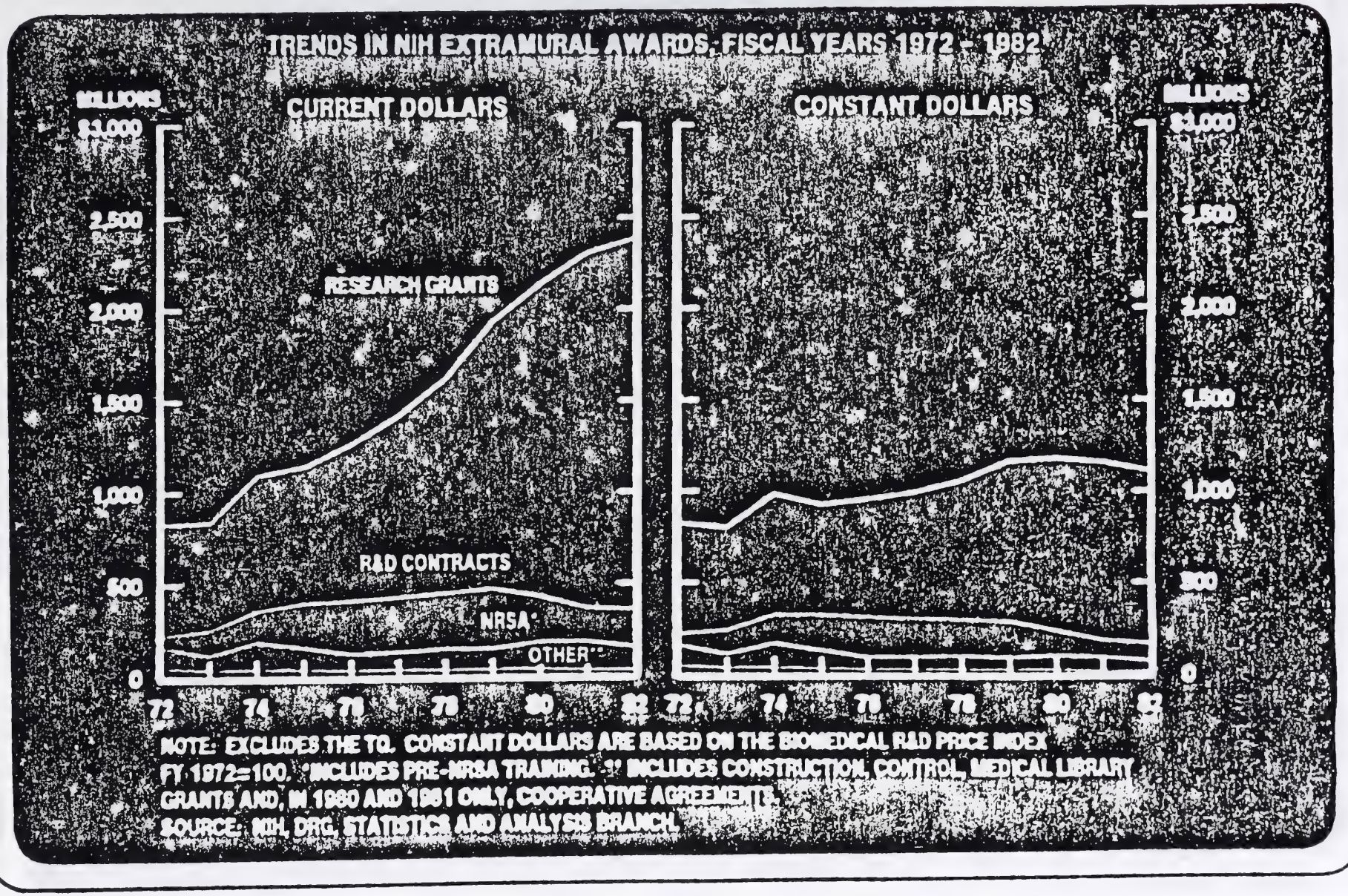
*PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Jud 3

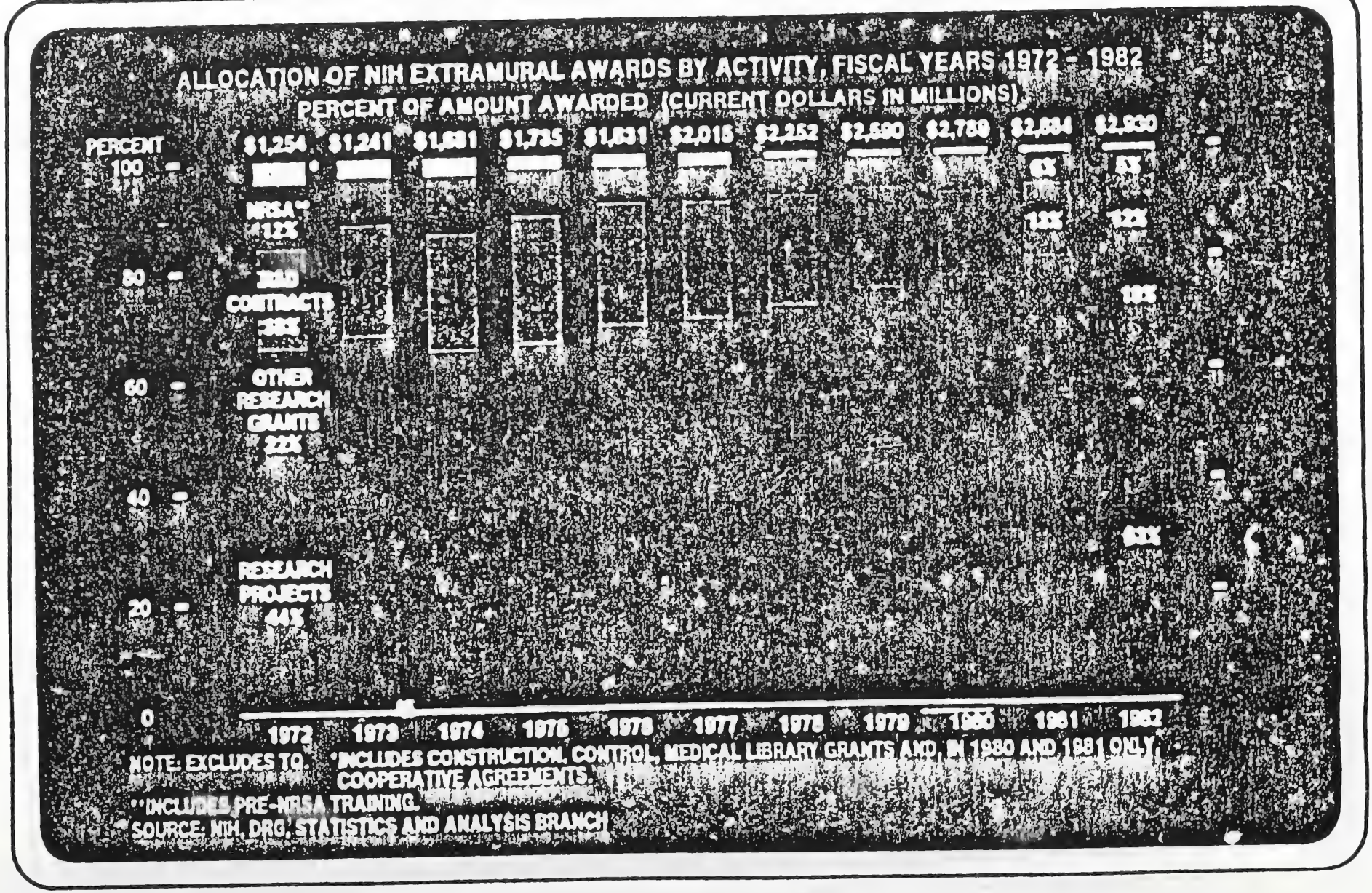
Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)




TRENDS IN NIH EXTRAMURAL AWARDS: FISCAL YEARS 1972 - 1982
CURRENT DOLLARS
CONSTANT DOLLARS
MILLIONS
$3,000
2,500
2,000
1,500
1,000
500
0
RESEARCH GRANTS
R&D CONTRACTS
NRSA*
OTHER**
72
74
76
78
80
82
NOTE: EXCLUDES THE TQ. CONSTANT DOLLARS ARE BASED ON THE BIOMEDICAL R&D PRICE INDEX FY 1972=100. *INCLUDES PRE-NRSA TRAINING. **INCLUDES CONSTRUCTION, CONTROL, MEDICAL LIBRARY GRANTS AND, IN 1980 AND 1981 ONLY, COOPERATIVE AGREEMENTS.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

Rm 1


ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972 - 1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)
PERCENT
100
80
60
40
20
0
$1,254
$1,241
$1,531
$1,735
$1,931
$2,015
$2,252
$2,590
$2,789
$2,884
$2,930
NRSA** 12%
CONTRACTS 29%
OTHER RESEARCH GRANTS 22%
RESEARCH PROJECTS 44%
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
NOTE: EXCLUDES TO
*INCLUDES CONSTRUCTION, CONTROL, MEDICAL LIBRARY GRANTS AND, IN 1980 AND 1981 ONLY, COOPERATIVE AGREEMENTS.
**INCLUDES PRE-NRSA TRAINING.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

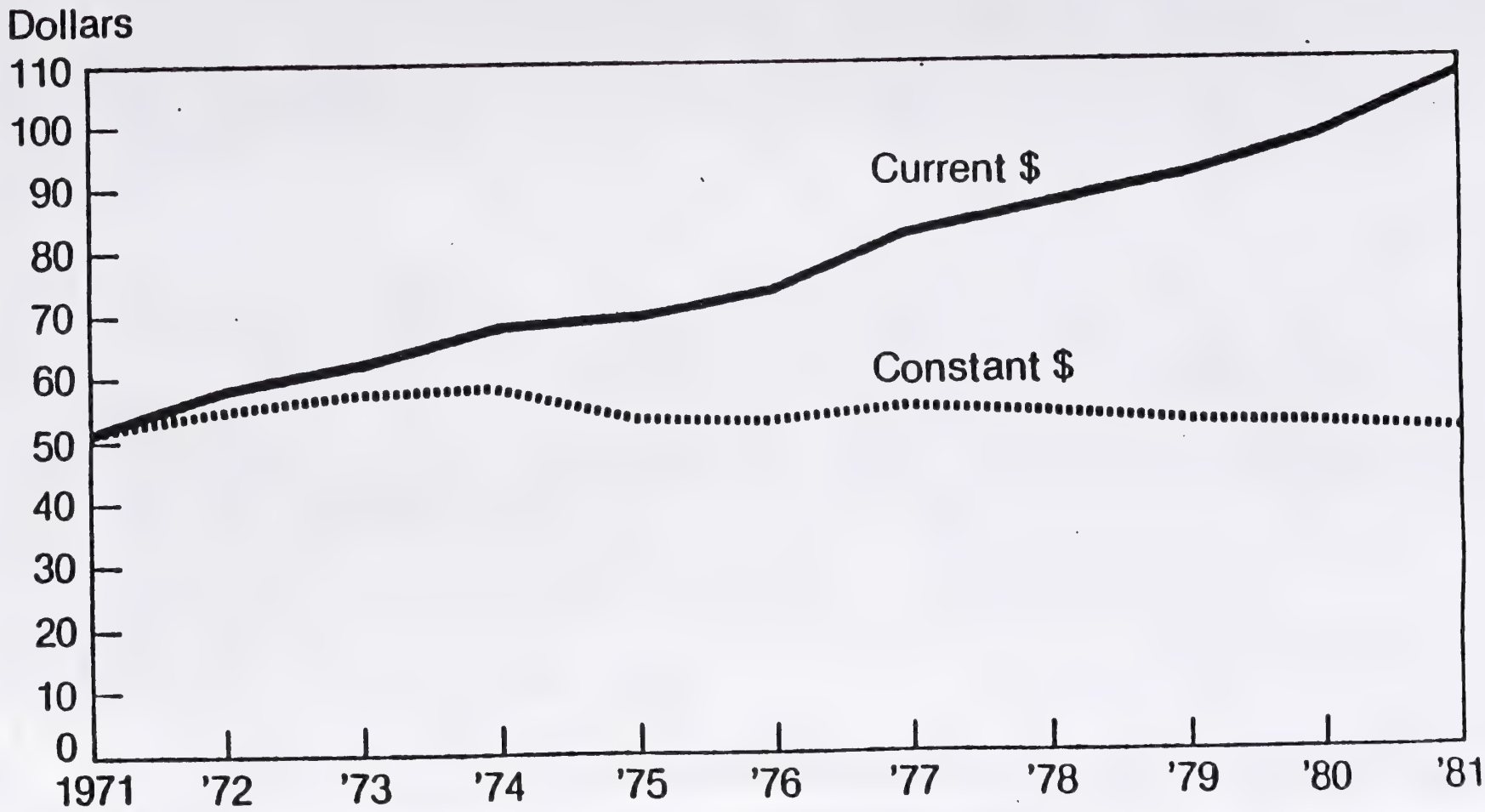
Rauh

Slide

SLIDE 5

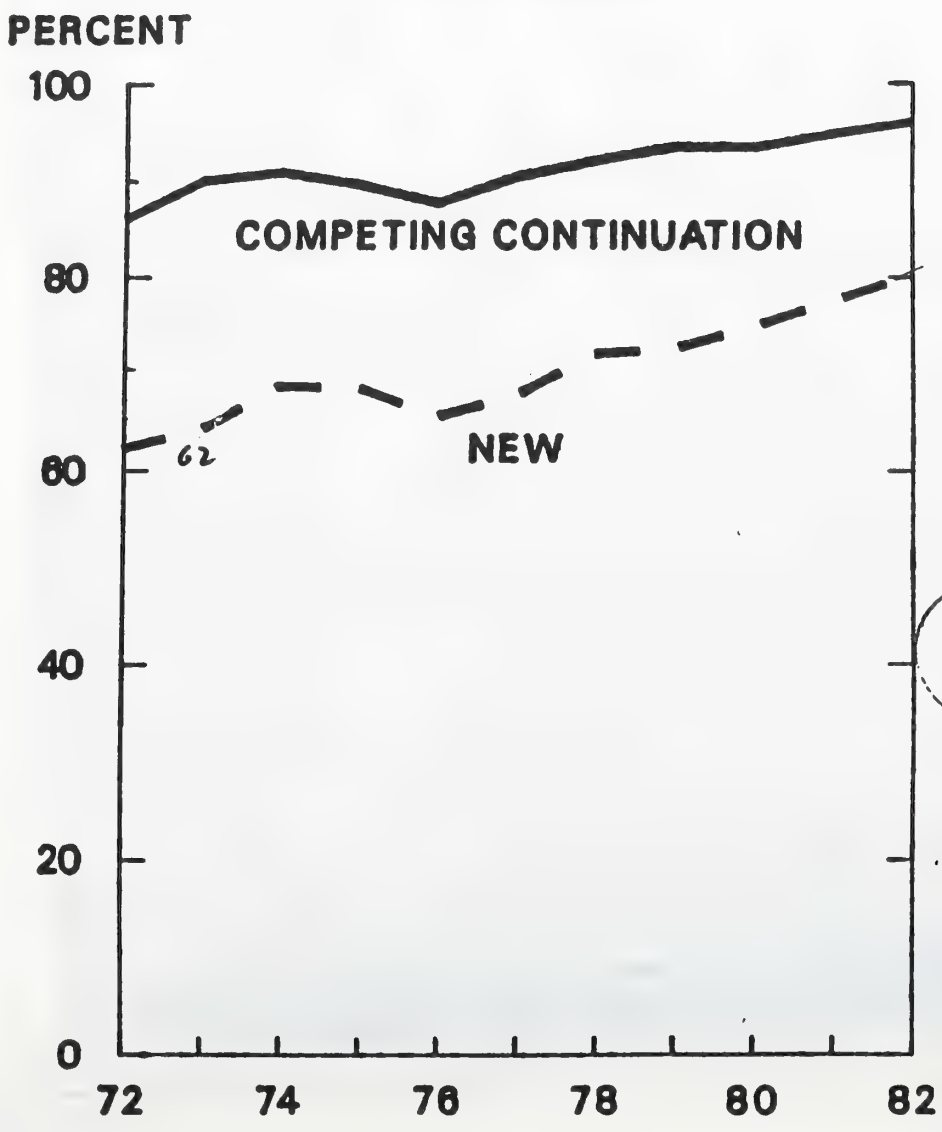
Average Research Project Grant, 1971-81

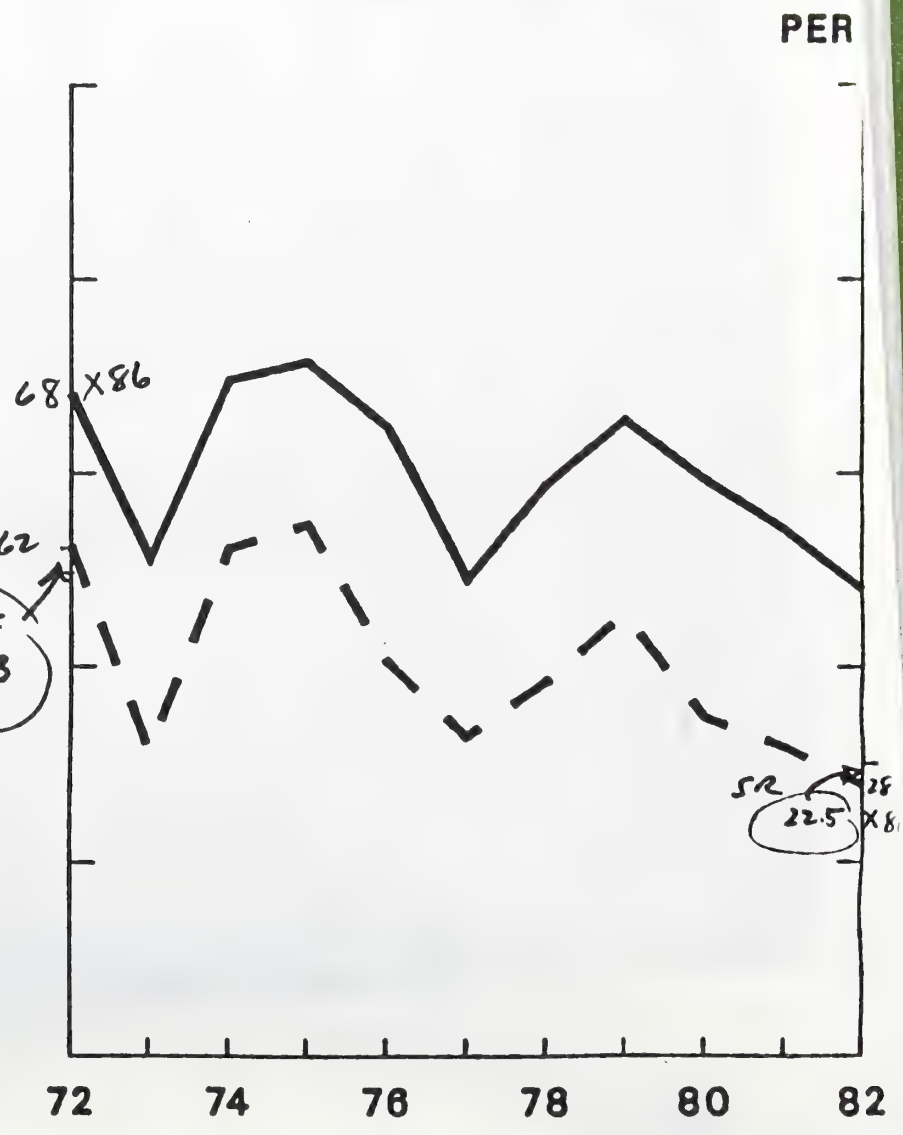
In Current and Constant Dollars (Thousands)



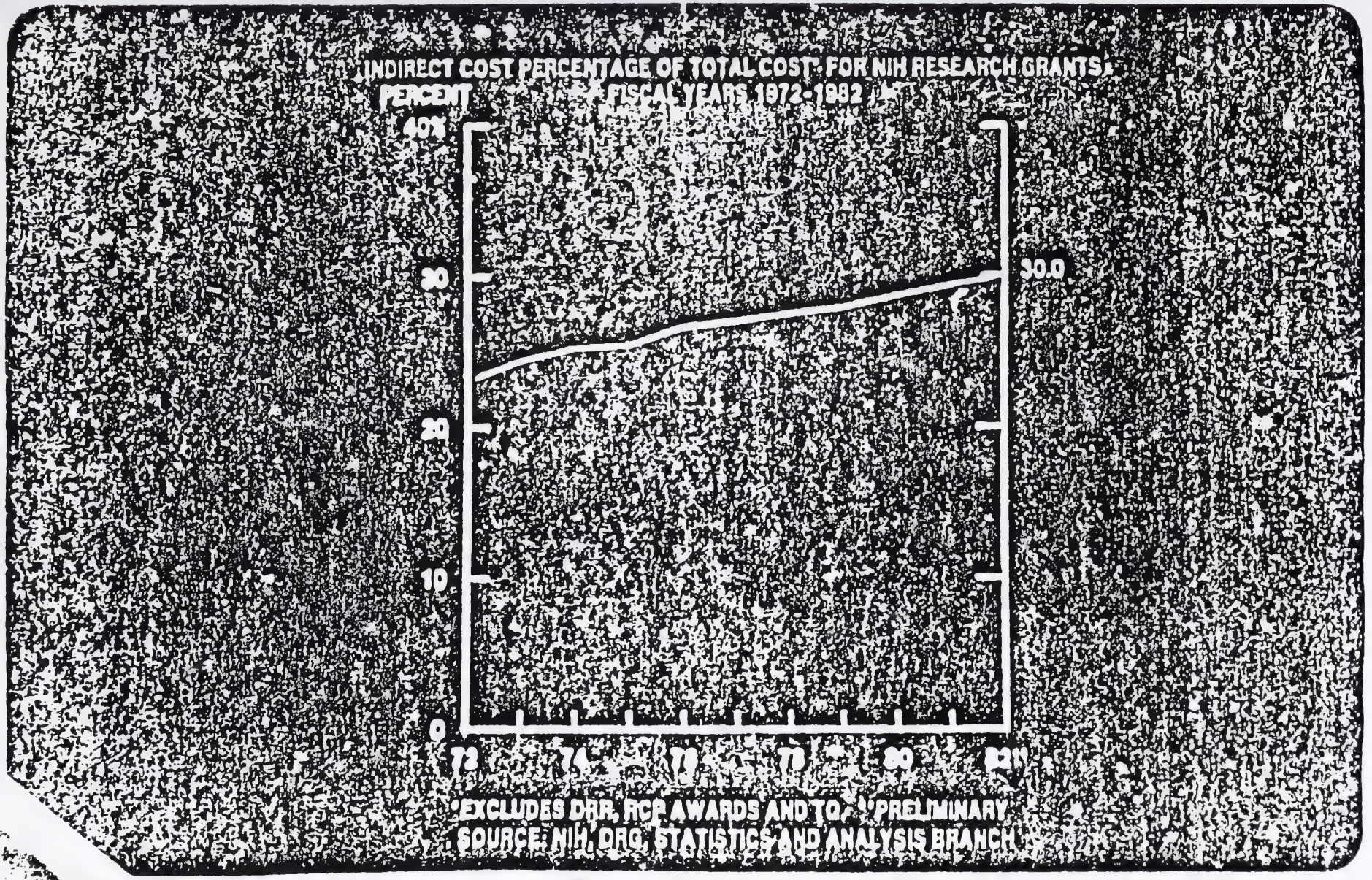
...IL RECOMMENDED FOR ... PROVAL AND AWARD RATES FOR NUMI
N...H RESEARCH PROJECT APPLICATIONS BY TYPE, FISCAL YEAR 1972-

Slide 7



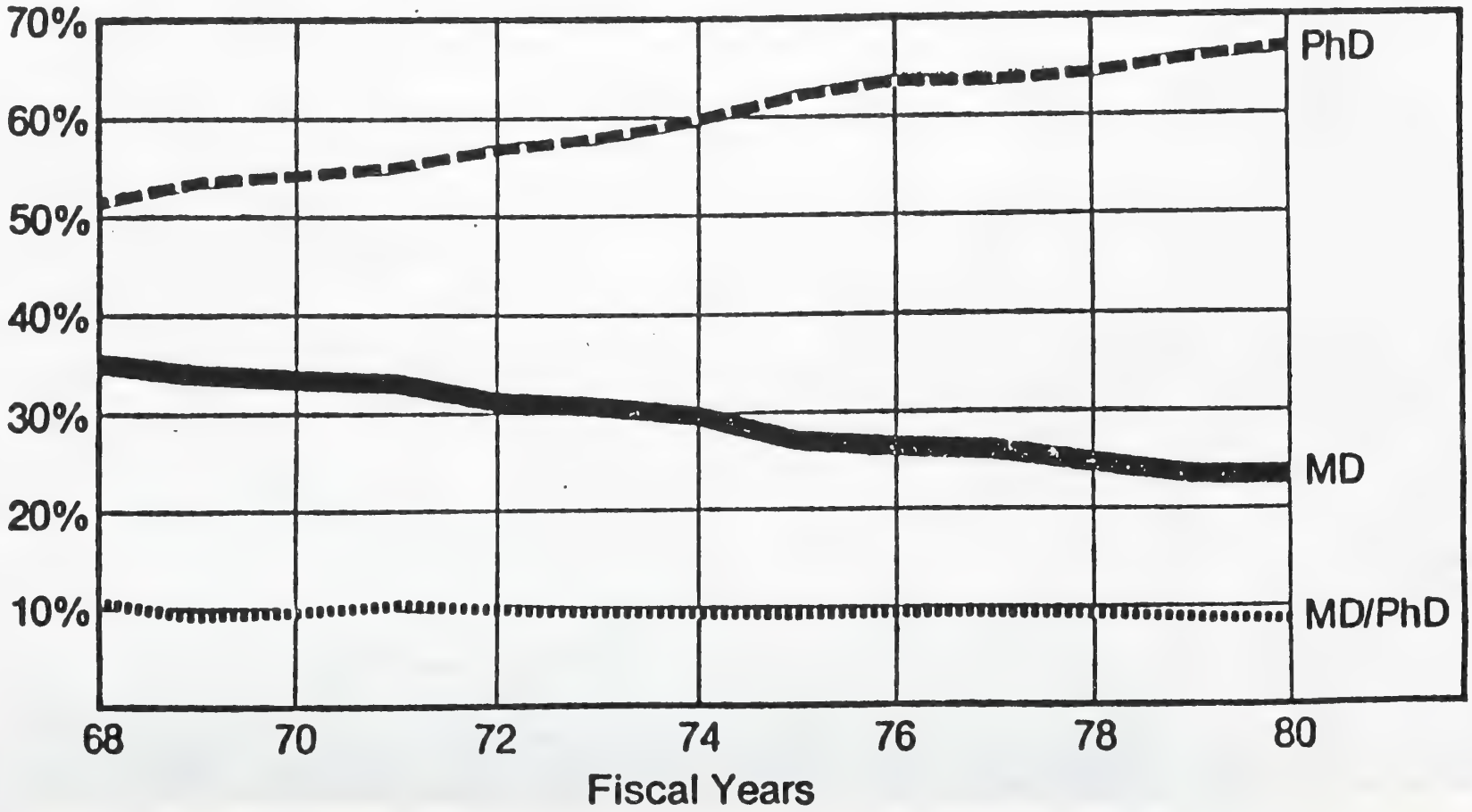


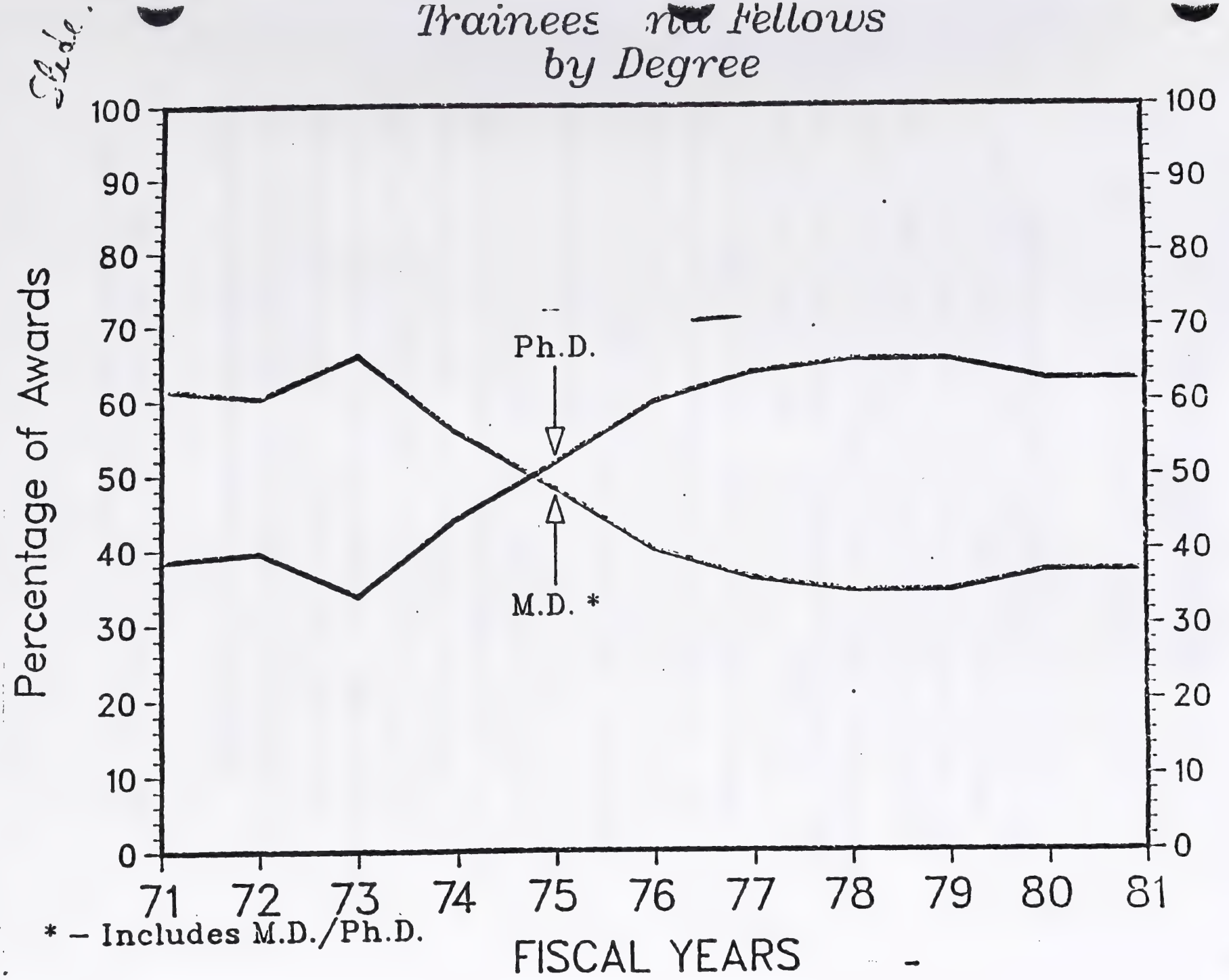
NOTE: DATA BASED ON ...


INDIRECT COST PERCENTAGE OF TOTAL COST* FOR NIH RESEARCH GRANTS
FISCAL YEARS 1972-1982
PERCENT
40%
30
20
10
0
30.0
72
74
77
80
82
*EXCLUDES DRR, RCR AWARDS AND TO
PRELIMINARY
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Slide 9

P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants




Trainees and Fellows
by Degree
Percentage of Awards
100
90
80
70
60
50
40
30
20
10
0
Ph.D.
M.D. *
71
72
73
74
75
76
77
78
79
80
81
FISCAL YEARS
* – Includes M.D./Ph.D.

WESTERN ASSOCIATION OF PHYSICIANS*

Remarks by

James B. Wyngaarden, M.D.**

I AM PLEASED TO BE HERE TODAY TO EXPLORE WITH YOU A VERY IMPORTANT ELEMENT OF THIS COUNTRY'S EFFORT IN SCIENCE, MEDICINE, AND HEALTH--THAT IS, THE STATUS OF THE PHYSICIAN-SCIENTIST. THIS WAS A SUBJECT OF INTEREST TO ME LONG BEFORE I CAME TO THE NIH. A FEW YEARS AGO I SPOKE TO THE ASSOCIATION OF AMERICAN PHYSICIANS ON THE CLINICAL INVESTIGATOR AS AN ENDANGERED SPECIES. MY REMARKS TODAY EXTEND AND AMPLIFY THOSE COMMENTS.

THE FUTURE OF BIOMEDICAL SCIENCE REQUIRES CREATIVITY AND EXCELLENCE IN BOTH BASIC AND CLINICAL RESEARCH. FOR MANY YEARS NIH HAS TRIED TO IMPRESS UPON THE PUBLIC AND THE CONGRESS THE IMPORTANCE OF SUPPORT FOR BOTH AREAS.

OVER THE YEARS, WE HAVE MADE A CASE FOR THE IMPORTANCE OF BUILDING A STORE OF FUNDAMENTAL BIOMEDICAL KNOWLEDGE, AND WE HAVE BEEN SUCCESSFUL. GOVERNMENT SUPPORT OF BASIC RESEARCH IS NOW A NATIONAL PRIORITY. GEORGE KEYWORTH, PRESIDENTIAL SCIENCE ADVISOR[1] IN A RECENT SPEECH EMPHASIZED, "BASIC RESEARCH WARRANTS GOVERNMENT SUPPORT BECAUSE IT IS AN INVESTMENT IN THE FUTURE--IN A BETTER QUALITY OF LIFE, BETTER SECURITY, A BETTER ECONOMY, AND SIMPLY BETTER UNDERSTANDING."

THERE HAS BEEN A BURGEONING OF BASIC KNOWLEDGE IN THE PAST DECADE WHICH HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH, YET A DIMINISHING SHARE OF PHYSICIANS IS INTERESTED IN APPLYING THEMSELVES TO THE CLINICAL RESEARCH NEEDS OF THE FUTURE. THIS IS A MATTER OF GREAT CONCERN.

THE FUTURE OF CLINICAL RESEARCH IS AN OBLIGATION OF THE NIH, THIS ORGANIZATION, AND THE MEDICAL SCHOOLS. IT IS UP TO US TO PORTRAY THE SATISFACTION THAT CAN COME FROM CLINICAL RESEARCH AS A CAREER. FOR THERE ARE DISINCENTIVES FOR YOUNG PEOPLE IN THE THROES OF MAKING CAREER DECISIONS. WE NEED TO LET YOUNG PEOPLE KNOW THAT IN CLINICAL RESEARCH THERE IS OPPORTUNITY NOT ONLY TO CONTRIBUTE DIRECTLY TO IMPROVING HEALTH AND SAVING LIVES BUT ALSO THE CHANCE TO EXPERIENCE THE EXCITEMENT THAT COMES FROM DISCOVERY.

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*Twenty-Eighth Annual Meeting, Carmel, California, February 8, 1983

**Director, National Institutes of Health, PHS

IN HIS BOOK "EXCELLENCE: CAN WE BE EQUAL AND EXCELLENT TOO?"[2] JOHN GARDNER REMARKED THAT THE INFLUX OF NEW PEOPLE INTO A GIVEN FIELD IN LARGE PART DEPENDS UPON THE MORALE OF THAT FIELD. A MAJOR COMPONENT OF OUR COLLECTIVE MORALE IS THE OPTIMISM AND ENCOURAGEMENT THAT WE CAN BRING TO THOSE ON THE BRINK OF DECISION.

IN A RECENT SURVEY[3] OF SENIOR MEDICAL STUDENTS BY THE AAMC, STUDENTS WHO EXPRESSED AN INTENTION OF CHOOSING A RESEARCH CAREER SELECTED AS ONE OF THE THREE MOST IMPORTANT MOTIVATING FACTORS "RESEARCH EXPERIENCE WHILE A PREMEDICAL OR MEDICAL STUDENT." (THE OTHER TWO FACTORS WERE "OPPORTUNITY TO WORK IN AN ACADEMIC COMMUNITY" AND "CHALLENGE OF SEARCH FOR NEW KNOWLEDGE.")

IT IS THE EARLY EXPOSURE TO THE RESEARCH PROCESS, NOT NECESSARILY EXPOSURE TO A PARTICULAR FIELD OF RESEARCH THAT IS ESSENTIAL. MANY INVESTIGATORS WHO HAVE ACHIEVED RECOGNITION IN A GIVEN FIELD DID THEIR FIRST WORK IN AN ENTIRELY DIFFERENT AREA. FOR EXAMPLE, CARLETON GAJDUSEK--WHO WON A NOBEL PRIZE FOR SLOW VIRUS RESEARCH--DID HIS FIRST WORK SYNTHESIZING A LARGE SERIES OF HALOGENATED ARYLOXYACETIC ACIDS (LATER PUT INTO COMMERCIAL USE AS WEED KILLER). FRANCIS CRICK STARTED IN EXPERIMENTAL AND THEORETICAL PHYSICS-- SPECIFICALLY, BUILDING AN APPARATUS WITH WHICH TO MEASURE THE VISCOSITY OF WATER AT TEMPERATURES ABOVE 100 DEGREES CELSIUS.

WHAT IS NEEDED IS EXPOSURE TO THE RESEARCH ATMOSPHERE, A GOOD ROLE MODEL, AND A TASTE OF DISCOVERY AND EXCITEMENT TO INSPIRE THE STUDENT OR HOUSE OFFICER TO RESEARCH.

I HAVE SPOKEN GENERALLY OF MY CONCERN ABOUT CLINICAL RESEARCH. SOME QUANTITATIVE DATA MAY SERVE TO EMPHASIZE SOME OF THE CURRENT STRESSES ON THE SYSTEM.

SLIDE 1 - P.I.'S HOLDING M.D., PH.D. OR MD/PHD DEGREES AS A PERCENTAGE OF ALL P.I.'S ON R01 GRANTS.

THIS SLIDE SHOWS M.D., PH.D. AND MD/PHD PRINCIPAL INVESTIGATORS AS A PERCENTAGE OF ALL PI'S. THE PERCENTAGE OF PH.D.'S HAS RISEN STEADILY OVER THE YEARS, WHILE THE PERCENTAGE OF M.D.'S HAS EQUALLY STEADILY FALLEN. MD/PHD'S HAVE BARELY HELD EVEN.

BETWEEN 1968 AND 1980, THE NUMBER OF AWARDS TO PH.D.'S INCREASED BY APPROXIMATELY 3,500, WHILE PHYSICIAN-SCIENTISTS EXPERIENCED VIRTUALLY NO GROWTH AS R01 GRANT HOLDERS. EXPRESSED AS A PERCENTAGE, THE PHYSICIAN-SCIENTISTS' SHARE (MD PLUS MD/PHD) OF TOTAL AWARDS DECREASED FROM ABOUT 45 PERCENT TO ABOUT 32 PERCENT.

SLIDE 2 - NUMBER OF PRINCIPAL INVESTIGATORS ON ALL R01 GRANTS HOLDING M.D., PH.D. OR MD/PHD DEGREES.

THIS SLIDE SHOWS THAT THE NUMBER OF GRANTS GOING TO M.D.'S FELL FROM ABOUT 3,400 IN 1968 TO ABOUT 2,500 IN 1973. THERE HAS BEEN SOME RECOVERY SINCE BUT THE NUMBER WAS STILL BELOW 3,000 IN 1980. MD/PHD'S (AND THESE, OF COURSE, ARE IN MUCH SMALLER NUMBERS) ARE HOLDING RATHER STEADY. THE RISE IN AWARDS TO PH.D.'S COINCIDED WITH THE RAPID EXPANSION OF THE NCI AND THE LARGE THRUST INTO MANY AREAS OF BASIC SCIENCE.

SLIDE 3 - NUMBER OF MD PRINCIPAL INVESTIGATORS ON ALL R01 GRANTS COMPARED WITH THE NUMBER OF MD'S WHO GRADUATED 11 YEARS PREVIOUSLY.

IN ORDER TO CONSTRUCT THIS SLIDE, WE DISPLAYED THE NUMBER OF M.D.'s SERVING AS PRINCIPAL INVESTIGATORS ON NIH INVESTIGATOR-INITIATED GRANTS FROM 1968 TO 1980. AGAINST THAT, WE PLOTTED THE NUMBER OF M.D. GRADUATES FOR EACH YEAR STARTING IN 1957. THE 11-YEAR OFFSET REFLECTS THE FACT THAT ON AVERAGE, THE M.D. IN RESEARCH DOES NOT RECEIVE HIS OR HER FIRST INDEPENDENT RESEARCH GRANT UNTIL 11 YEARS AFTER GRADUATION. AS THE SLIDE SHOWS, THE RATIO BETWEEN M.D. PRINCIPAL INVESTIGATORS AND NUMBER OF M.D. GRADUATES HAS NOT WIDENED DRAMATICALLY OVER THE YEARS SHOWN. HOWEVER, SINCE MEDICAL SCHOOL ENROLLMENT INCREASED GREATLY AFTER 1968, WE SUSPECT THAT THIS GAP MAY SOON ENLARGE.

BECAUSE CAREER PARTICIPATION IN RESEARCH FOR A PHYSICIAN IS USUALLY EQUATED WITH A FACULTY APPOINTMENT TO A MEDICAL SCHOOL, WE CAN LOOK TO DATA ON MEDICAL SCHOOL FACULTIES FOR SOME CLUES ABOUT THE FUTURE. A RECENT ANALYSIS BY NIH[4] SHOWS THAT THE PERCENTAGE OF ALL NEWLY-HIRED PHYSICIANS WITH POSTDOCTORAL RESEARCH TRAINING FELL FROM 28 PERCENT IN 1970 TO A LOW OF 20 PERCENT IN 1979. IT HAS SINCE RISEN TO 25 PERCENT IN 1981. THIS COULD BE A POSITIVE SIGN FOR THE FUTURE OF CLINICAL RESEARCH.

AT THIS TIME, NIH CANNOT FULLY ASSESS THE NUMBERS OF PHYSICIANS INVOLVED IN NIH-SUPPORTED RESEARCH. WE THINK THAT MANY PARTICIPATE ON LARGE PROGRAM PROJECT GRANTS IN ROLES OTHER THAN PRINCIPAL INVESTIGATORS AND THUS CANNOT BE COUNTED BY OUR TRACKING SYSTEMS. MOST LIKELY THEY ARE SUBPROJECT DIRECTORS OR PARTICIPANTS IN CLINICAL PORTIONS OF THE MULTIPART GRANTS.

IT IS VERY IMPORTANT TO STRESS, HOWEVER, THAT WHILE PH.D. PARTICIPATION IN THE NIH RESEARCH GRANTS SYSTEM IS OUTPACING THAT OF M.D.'S, THE ABSOLUTE LEVEL OF M.D. GRANT ACTIVITY IS REMAINING RELATIVELY CONSTANT.

THE AWARD RATES FOR M.D.'S--THAT IS, THE RATIO BETWEEN M.D. AWARDS AND STUDY-SECTION APPROVED APPLICATIONS FROM M.D.'S--HAVE REMAINED FAIRLY STABLE SINCE 1977, AS SEEN ON THE NEXT SLIDE.

SLIDE 4 - APPROVAL, AWARD, AND SUCCESS RATES FOR COMPETING R01 APPLICATIONS: 1974-80.

THE APPROVAL RATE FOR APPLICATIONS SUBMITTED BY PH.D. INVESTIGATORS HAS BEEN FOUR OR FIVE PERCENTAGE POINTS AHEAD OF RATES FOR M.D. INVESTIGATORS. BUT OF THOSE APPLICATIONS APPROVED BY STUDY SECTIONS, THE AWARD RATES FOR M.D. AND PH.D. PRINCIPAL INVESTIGATORS HAVE BEEN VIRTUALLY THE SAME. THE SUCCESS RATE--THAT IS, THE CHANCE OF ACTUALLY BEING FUNDED FOR AN APPLICATION SUBMITTED--IS SOMEWHAT HIGHER FOR PH.D.'S THAN M.D.'S.

SLIDE 5 - SUCCESS OF NEW APPLICANTS ON NIH RESEARCH PROJECTS (TYPE 1 R01 APPLICANTS BY TYPE OF DEGREE OF P.I.).

WHEN ONE LOOKS AT THE SUCCESS OF NEW APPLICANTS ALONE, ONE FINDS THAT THERE HAS BEEN A DIVERGENCE SINCE 1974, WITH NEW M.D./PH.D. APPLICANTS COMPETING MOST SUCCESSFULLY, NEW PH.D. APPLICANTS NEXT, AND M.D. APPLICANTS COMPETING PROGRESSIVELY LESS WELL.

THIS TREND IS EVEN MORE DRAMATIC WHEN EXPRESSED IN COMPARISON WITH THE AVERAGE SUCCESS RATE OF ALL RESEARCH GRANT APPLICATIONS OF THAT YEAR, WHICH IN THE NEXT SLIDE HAS BEEN GIVEN A SCORE OF 1.0.

SLIDE 6 - SUCCESS RATE OF NEW M.D., PH.D., AND MD/PHD APPLICANTS COMPARED WITH AVERAGE SUCCESS RATES OF ALL TYPE 1 R01 APPLICANTS IN THE SAME YEAR.

NOTE THAT, INCREASINGLY, THE GREATEST SUCCESS IS OBTAINED BY THE MD/PHD APPLICANT, FOLLOWED BY THE PH.D. APPLICANT AT SOMEWHAT ABOVE THE AVERAGE RATE, AND BY THE M.D. APPLICANT WHO IS INCREASINGLY BELOW THE AVERAGE.

ONE FACTOR THAT MAY BE PLAYING A ROLE IN THE RECORD FOR M.D. APPLICANTS IS THE FACT THAT APPLICATIONS FOR CLINICAL RESEARCH TEND TO FARE LESS WELL THAN BASIC SCIENCE APPLICATIONS IN THE NIH GRANT SYSTEM.

CLINICAL RESEARCH APPLICATIONS--THOSE INVOLVING HUMAN SUBJECTS--ARE MORE OFTEN DISAPPROVED AND MORE OFTEN ASSIGNED POORER PRIORITY SCORES THAN ARE APPLICATIONS IN WHICH NO HUMAN SUBJECTS ARE INVOLVED.

AS THE NEXT SLIDE INDICATES, APPROVAL RATES FOR STUDIES WHICH DO NOT INVOLVE HUMAN SUBJECTS ARE SUBSTANTIALLY HIGHER THAN THOSE FOR STUDIES WHICH DO.

SLIDE 7 - COMPETING R01 APPLICATIONS 1975-1981: HUMAN SUBJECTS/NO HUMAN SUBJECTS.

IN ORDER TO DISCOVER WHY APPLICATIONS TO NIH FOR GRANTS TO CONDUCT CLINICAL RESEARCH MAY EITHER BE DISAPPROVED OR RECEIVE POOR PRIORITY SCORES IN THE REVIEW PROCESS, THE DIVISION OF RESEARCH GRANTS RECENTLY EXAMINED 256 APPLICATIONS RATED BY 13 DIFFERENT STUDY SECTIONS.[5] FOR THE STUDY, CLINICAL RESEARCH WAS NARROWLY DEFINED AS RESEARCH INVOLVING HUMAN SUBJECTS THAT INCLUDED A DOCTOR-PATIENT RELATIONSHIP. THE DATA CONFIRMED THE WIDESPREAD IMPRESSION THAT CLINICAL RESEARCH HAS A TOUGHER TIME IN THE PEER REVIEW SYSTEM.

SLIDE 8 - SHORTCOMINGS IN POORLY-RATED OR DISAPPROVED NIH GRANT APPLICATIONS.

THIS SLIDE SHOWS THE SHORTCOMINGS IN POORLY RATED OR DISAPPROVED GRANT APPLICATIONS FOR CLINICAL RESEARCH. IT IS BOTH INTERESTING AND IMPORTANT TO NOTE THAT INVESTIGATOR QUALIFICATIONS AND RESOURCES AVAILABLE AT THEIR INSTITUTIONS PLAYED A VERY MINOR ROLE IN POOR RATING. FLAWS IN RESEARCH DESIGN AND CONCEPTION OF THE HYPOTHESIS LED TO POOR SCORES FROM REVIEWERS.

THE MOST FREQUENT DEFICIENCIES--FAULTY HYPOTHESES AND INAPPROPRIATE EXPERIMENTAL DESIGN--WERE THE SAME FLAWS THAT WERE CITED IN THE BASIC RESEARCH PROPOSALS THAT WERE DISAPPROVED.

THE FACILE EXPLANATION OF THE GREATER INHERENT DIFFICULTY OF WORKING WITH HUMAN SUBJECTS MAY NOT BE THE ENTIRE ANSWER TO THE LOWER APPROVAL RATES FOR PHYSICIANS. SCIENCE HAS BECOME COMPLEX, THE METHODS INTRICATE AND THE TRAINING PERIOD LONG SO THAT THE PHYSICIAN, EVEN AFTER TWO OR THREE YEARS OF FELLOWSHIP, REMAINS LESS WELL-TRAINED THAN THE PH.D. SCIENTIST WHO HAS BEEN TRAINING FOR A RESEARCH CAREER SINCE THE BACCALAUREATE. THUS THE ADEQUACY OF THE TRAINING OPPORTUNITY MUST BE A PARAMOUNT CONSIDERATION FOR THE YOUNG PHYSICIAN.

IN MY VIEW, THE TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT FOR HIS OR HER WORK.

SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MODERN SCIENCE. CLINICAL RESEARCH REQUIRES EXPERIENCES NOT REPRESENTED IN MOST MEDICAL SCHOOL AND HOUSE STAFF EXPERIENCES. THE QUALITY OF A RESEARCH GRANT APPLICATION IS A REFLECTION OF THE COMPETENCE AND SOPHISTICATION OF THE INVESTIGATOR APPLICANT.

THE INTEGRAL RELATIONSHIP BETWEEN TRAINING AND RESEARCH SEEMS ALMOST SELF-EVIDENT, BUT I'D LIKE TO CITE AT LEAST ONE STUDY THAT SUPPORTS THIS CONTENTION. THE NIH HAS LOOKED AT HOW A RANDOM SAMPLE OF M.D.'S AND PH.D'S, WITH AND WITHOUT NIH/PHS SUPPORTED RESEARCH TRAINING, HAS FARED IN OBTAINING NIH COMPETING GRANTS FROM FISCAL YEARS 1967 TO 1978. THE NEXT SLIDE SHOWS THE SUCCESS RATES OF THESE POPULATIONS, THAT IS, THE RATIO OF FUNDED COMPETING RESEARCH GRANT APPLICATIONS TO ALL SUCH APPLICATIONS.

SLIDE 9 - AVERAGE SUCCESS RATES ON NIH COMPETING RESEARCH GRANT APPLICATIONS BY DOCTORAL DEGREE AND NIH/PHS TRAINING SUPPORT, FY-1967-1978.

THIS ANALYSIS FOUND THAT M.D.'S WITH NIH-SUPPORTED TRAINING HAD AN AVERAGE SUCCESS RATE OF 36.5 PERCENT VERSUS 25 PERCENT FOR M.D.'S WITHOUT SUCH TRAINING. A SIMILARLY LARGE DIFFERENCE BASED ON TRAINING WAS FOUND IN THE AVERAGE SUCCESS RATES FOR PH.D.'S.

OF COURSE, SUCCESS RATE--THAT IS, AN INDIVIDUAL'S CHANCE OF ACTUALLY BEING FUNDED FOR A GRANT APPLICATION SUBMITTED--IS ULTIMATELY DEPENDENT UPON THE NIH APPROPRIATION. BECAUSE WE FUND APPLICATIONS ACCORDING TO MERIT, AS DESIGNATED BY THE PRIORITY SCORE, THE LARGER THE APPROPRIATION, THE GREATER NUMBER OF MERITORIOUS APPLICATIONS WE CAN FUND. AS THE NEXT SLIDE SHOWS, THE NIH BUDGET HAS BEEN GROWING IN TERMS OF ACTUAL DOLLARS.

SLIDE 10 - TOTAL NIH APPROPRIATIONS, 1972-82 IN CURRENT AND CONSTANT DOLLARS (MILLIONS).

HOWEVER, IN THE PAST DECADE, THE GROWTH IN SUPPORT HAS BEEN MORE APPARENT THAN REAL--THE 1979 APPROPRIATION OF $3.2 BILLION REPRESENTS AN ALL-TIME HIGH IN CONSTANT DOLLARS, BUT WAS WORTH ONLY $1.92 BILLION IN 1972 DOLLARS. BETWEEN 1979 AND 1982, THE CONSTANT DOLLAR LEVEL FELL BY 12 PERCENT. A SLIGHT INCREASE TO THE 1983 LEVEL OF $1.77 BILLION INDICATES THAT FOR THE PRESENT AT LEAST, THE DECLINE IN PURCHASING POWER HAS LEVELED OFF. BETWEEN 1972 AND 1982, AN INCREASE OF ABOUT 15 PERCENT WAS ALMOST EXACTLY MATCHED BY THE INCREASE IN INDIRECT COSTS. THEREFORE, THE DOLLARS AVAILABLE FOR THE DIRECT COSTS OF RESEARCH HAVE BEEN ESSENTIALLY CONSTANT FOR A DECADE, AT A TIME WHEN THE NUMBER OF CAPABLE AND MATURING SCIENTISTS HAS MUCH INCREASED AND SCIENTIFIC OPPORTUNITY HAS BECOME GREATER THAN EVER BEFORE.

A WEEK AGO PRESIDENT REAGAN PRESENTED HIS BUDGET REQUEST FOR 1984. AS YOU KNOW, IT REFLECTS THE GENERAL CONCERN OVER THE SIZE OF THE DEFICIT AND CALLS FOR REDUCTIONS IN THE AMOUNTS ALLOCATED TO MANY SO-CALLED "CONTROL-LABLE" PROGRAMS. BIOMEDICAL RESEARCH IS SUCH A PROGRAM. THE 1984 REQUEST FOR NIH IS $4.077 BILLION--AN INCREASE OF $73 MILLION OR 1.8 PERCENT OVER THE CURRENT LEVEL. IN THE ABSENCE OF INTERNAL ADJUSTMENTS, THE REQUESTED BUDGET WOULD PERMIT NIH TO SUPPORT ONLY AN ESTIMATED 3,676 NEW AND COMPETING PROJECT GRANTS AS COMPARED WITH THE ESTIMATED 1983 LEVEL OF 4,914. WITH THE

INCLUSION OF NONCOMPETING AWARDS, THE TOTAL NUMBER OF RESEARCH PROJECT GRANTS WOULD BE 15,236. HOWEVER, WE CURRENTLY EXPECT TO FUND 4,105 NEW AND COMPETING GRANTS AND 15,665 ALTOGETHER, FOLLOWING SOME INTERNAL RE-BUDGETING. NEGOTIATIONS WITH THE OFFICE OF MANAGEMENT AND BUDGET (OMB) ARE CONTINUING.

ALTHOUGH IN RETROSPECT A PROGRESSIVE SHIFT OF NIH DOLLARS AMONG FUNDING INSTRUMENTS BEGAN IN ABOUT 1974 WHEN THE NIH BUDGET BEGAN TO LEVEL OFF, THE FIRST SUBSTANTIAL DECLINE IN CONSTANT DOLLAR BUDGET IN 1980 SIGNALLED THAT THE TIME HAD COME FOR A REASSESSMENT OF PROGRAMS AND POLICIES IN ORDER TO MAINTAIN THE MOMENTUM OF SCIENTIFIC INQUIRY IN THE FACE OF LIMITED RESOURCES.

THE ANSWER WAS AN ARTICULATED POLICY OF "STABILIZATION," WHICH MADE FORMAL SEVERAL TRENDS ALREADY UNDERWAY. UNDER THIS POLICY. NIH SET AS MINIMAL GOALS THE FUNDING OF 5,000 NEW AND COMPETING GRANTS AND 10,000 TRAINEES AND FELLOWS PER YEAR.

ONE FUNDAMENTAL PRINCIPLE UNDERLYING THIS EFFORT IS THAT INVESTIGATOR-INITIATED RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY. THROUGH COMPETING RESEARCH PROJECTS, WE TAP THE BEST MINDS AND MOST CREATIVE IDEAS AND WEIGH THEM THROUGH PEER REVIEW. ANOTHER IMPORTANT ELEMENT IS THE NEED TO ASSURE A CONTINUING SUPPLY OF WELL-TRAINED SCIENTISTS TO MEET NATIONAL HEALTH GOALS.

THUS, UNDER THIS STABILIZATION POLICY, INVESTIGATOR-INITIATED RESEARCH PROJECTS AND RESEARCH TRAINING HAVE BEEN GIVEN TOP PRIORITY. THE CONGRESS HAS INDICATED ITS HEARTY ACCORD WITH THIS PRIORITY.

BUT THE STABILIZATION POLICY ALSO HAS ITS DOWN SIDE. IN ORDER TO FUND 5,000 NEW AND COMPETING PROJECTS, DOLLARS HAVE BEEN SHIFTED FROM OTHER MECHANISMS EACH YEAR SINCE 1974.

SLIDE 11 - ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1982.

WHILE THE PROPORTION OF THE NIH BUDGET ASSIGNED TO SUPPORT INVESTIGATOR-INITIATED RESEARCH PROJECTS HAS GROWN, OTHER MECHANISMS HAVE BEEN CURTAILED, ESPECIALLY NIH INITIATIVES TO EMPHASIZE SPECIAL AREAS OR ACTIVITIES AS IN CENTERS, OR TO ANSWER SPECIFIC QUESTIONS AS IN CLINICAL TRIALS. AFTER

SEVERAL TURNS OF THE RATCHET, MANY INSTITUTE DIRECTORS FEEL THAT FURTHER SHIFTS WOULD SERIOUSLY LIMIT THEIR ABILITY TO MEET OTHER PROGRAM GOALS AND TO MAINTAIN PROGRAM BALANCE. IF THE RATE OF INCREASE IN PERCENT OF THE EXTRAMURAL BUDGET DEVOTED TO RESEARCH GRANTS WERE TO CONTINUE, THIS CATEGORY WOULD REACH 100 PERCENT IN 1993!

AT THE HEART OF ALL THESE CONSIDERATIONS IS THE NEED TO STRETCH THE RESEARCH DOLLAR WITHOUT COMPROMISING THE QUALITY OF INVESTIGATION. OUR EMPHASIS ON QUALITY RATHER THAN ON DISTRIBUTION HAS CREATED SOME ANXIETY IN THE RESEARCH COMMUNITY AND HAS PROMPTED VARIED RESPONSES. DURING 1982, ALTHOUGH WE FUNDED 5,027 NEW AND COMPETING RESEARCH AWARDS, THIS FIGURE REPRESENTS ONLY ABOUT A THIRD OF APPROVED GRANT APPLICATIONS.

SLIDE 12 - COUNCIL RECOMMENDED FOR APPROVAL AND AWARD RATES.

WHILE WE SHARE A DEEP CONCERN FOR SCIENTISTS WHOSE DESERVING PROJECTS WE CANNOT FUND, WE FEEL THAT THE INTERESTS OF SCIENCE ARE BEST SERVED BY FUNDING THE MOST MERITORIOUS WORK AS JUDGED BY THE PEER REVIEW SYSTEM AND BY ASSURING THAT SUCH PROJECTS ARE ADEQUATELY FUNDED FOR THE EXECUTION OF THE STUDY.

HAVING GIVEN THIS BACKGROUND AND UPDATE ON THE NIH BUDGET SITUATION, I WOULD LIKE TO RETURN TO THE MATTER OF PHYSICIAN INVESTIGATORS. LET'S TAKE A QUANTITATIVE LOOK AT M.D. PARTICIPATION IN NIH EXTRAMURAL TRAINING PROGRAMS.

AS IS SHOWN ON THE NEXT SLIDE, M.D. PARTICIPATION IN RESEARCH TRAINING HAS DECREASED SUBSTANTIALLY SINCE 1971.

SLIDE 13 - NUMBERS OF NIH POSTDOCTORAL TRAINEES AND FELLOWS BY DEGREE.

THE NUMBERS OF M.D. TRAINEES AND FELLOWS FELL FROM ABOUT 4,600 TO ABOUT 1,900 BETWEEN FY 1971 AND 1981. OF COURSE, CESSATION OF FEDERAL SUPPORT FOR CLINICAL TRAINING IN THE EARLY 1970'S CONTRIBUTED TO THIS DECLINE.

DATA FROM 1975 TO THE PRESENT CORRESPOND TO THE INCEPTION AND DEVELOPMENT OF THE NRSA PROGRAM. HERE, WE SEE THE DECLINE IN M.D. PARTICIPATION CONTINUING TO FY 1976 AND THEN APPARENTLY LEVELING OFF. NOTE, HOWEVER, AT THE SAME TIME, PH.D. PARTICIPATION HAS GREATLY INCREASED.

THE DECLINE OF M.D.'S AS A PERCENTAGE OF NIH TRAINEES AND FELLOWS IS SHOWN IN THE NEXT SLIDE.

SLIDE 14 - PERCENTAGE OF NIH POSTDOCTORAL TRAINEES AND FELLOWS BY DEGREE.

IN 1971, ABOUT 60 PERCENT WERE M.D.'S AND MD/PHD'S. BY 1981, HOWEVER, THE PROPORTION OF PHYSICIANS HAD FALLEN BELOW 40 PERCENT. AN ALMOST MIRROR IMAGE DISPLAY IS SEEN FOR PH.D.'S.

THE CLINICAL INVESTIGATOR PROVIDES THE INDISPENSABLE LINK BETWEEN THE LABORATORY AND THE HUMAN BEING WHO IS THE ULTIMATE FOCUS OF ALL OF OUR ENDEAVORS. FOR THIS REASON, WE VIEW WITH GREAT CONCERN THE DECLINE IN THE NUMBER OF M.D.'S IN NIH-SUPPORTED RESEARCH TRAINING PROGRAMS FROM 4,100 IN 1968 TO ABOUT 1,900 IN 1980.

WHEN NIH PROGRAMS WERE MODIFIED IN 1974, (UNDER THE NATIONAL RESEARCH SERVICE AWARDS ACT, TO PROVIDE TRAINING EXCLUSIVELY FOR RESEARCH OR ACADEMIC DEVELOPMENT), A COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES RECOMMENDED THAT 2,800 CLINICAL RESEARCH TRAINING SLOTS BE OFFERED ANNUALLY--2,400 AS TRAINEESHIPS, AND 400 AS DIRECT FELLOWSHIPS. THIS FIGURE OF 2,800 CLINICAL TRAINING POSITIONS WAS NOT REACHED UNTIL 1980, BUT AT THAT TIME 900 OF THESE CLINICAL TRAINEESHIPS WERE HELD BY PH.D. TRAINEES, ONLY 1,900 BY M.D. TRAINEES. THE ACADEMY COMMITTEE HAS RECOMMENDED THAT AT LEAST 85 PERCENT OF THE TRAINEESHIPS IN THIS CATEGORY BE FILLED BY M.D.'S. SO BY EVERY YARD-STICK, WE ARE FAILING TO ATTRACT THE NUMBER OF QUALIFIED PHYSICIANS INTO RESEARCH TRAINING PERCEIVED TO BE DESIRABLE BY THE ACADEMY COMMITTEE. THIS BODES ILL FOR THE BALANCE BETWEEN M.D. AND PH.D. INVESTIGATORS DEEMED ESSENTIAL FOR COORDINATED PROGRESS IN BASIC SCIENCE AND CLINICAL RESEARCH.

MANY REASONS HAVE BEEN CITED IN EXPLANATION OF THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH. MOST MEDICAL SCHOOL CURRICULA PROVIDE LITTLE OR NO LABORATORY EXPERIENCE THAT IS REPRESENTATIVE OF MODERN DAY MEDICAL SCIENCE. THE RISE OF SPECIALTY FIELDS AND THE LENGTHENING OF POST-DOCTORAL TRAINING PROGRAMS HAVE EXTENDED THE CLINICAL TRAINING NECESSARY FOR BOARD CERTIFICATION. THE REQUIREMENTS OF MANY CERTIFICATION BOARDS ARE RATHER INFLEXIBLE AND CERTAINLY DO NOT ENCOURAGE THE POTENTIALLY CREATIVE PHYSICIAN TO ENTER RESEARCH TRAINING.

THE PAYBACK PROVISION OF THE NATIONAL RESEARCH SERVICE AWARD MAY ACT AS A DETERRENT FOR SOME POTENTIAL TRAINEESHIP APPLICANTS. PERHAPS DOMINATING THE ISSUES IS THAT OF THE FINANCIAL DISINCENTIVES, BOTH BETWEEN THE THIRD-YEAR RESIDENCY SALARY AND THE FIRST-YEAR TRAINEESHIP, WHICH NOW EXHIBITS AN AVERAGE GAP OF $4,500, AND THE SUBSTANTIALLY LARGER DIFFERENCES BETWEEN THE INCOME POSSIBILITIES IN RESEARCH AND IN PROCEDURE-ORIENTED PRACTICES OF MEDICINE. AND ESPECIALLY WHEN THE DEBT LOAD INCURRED BY THE GRADUATING STUDENT IS $20,000 OR MORE, THE CUMULATIVE FINANCIAL DISINCENTIVES ARE A MAJOR FACTOR IN DISSUADING POTENTIAL INVESTIGATORS FROM ENTERING THE FIELD.

FORTUNATELY, THIS GROWING PROBLEM HAS RECEIVED CONSIDERABLE ATTENTION IN THE CONGRESS. JUST A FEW MONTHS AGO WE RECEIVED THE REPORT OF THE HOUSE COMMITTEE ON APPROPRIATIONS REGARDING THE PROPOSED 1983 BUDGET FOR THE NIH[6]. PERMIT ME TO READ A PARAGRAPH:

> "THE COMMITTEE SHARES THE CONCERNS THAT HAVE BEEN EXPRESSED BY OFFICIAL AND PUBLIC WITNESSES ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS, ESPECIALLY AS ALL CLINICAL RESEARCH, INVOLVING HUMAN PATIENTS, MUST BE DONE BY--OR AT LEAST UNDER THE GUIDANCE AND SUPERVISION OF--A QUALIFIED PHYSICIAN. IT IS APPARENT AND UNDERSTANDABLE, THAT YOUNG PHYSICIANS CONSIDERING CAREERS IN HEALTH RESEARCH ARE OFTEN DISSUADED FROM APPLYING FOR RESEARCH TRAINING OR RESEARCH FELLOWSHIPS BY THEIR PERCEPTION OF THE INSTABILITY OF THE FEDERAL COMMITMENT TO RESEARCH AND BY THEIR AWARENESS THAT A RESEARCH CAREER REPRESENTS A SUBSTANTIAL FINANCIAL SACRIFICE WHEN COMPARED WITH ALMOST ANY FORM OF MEDICAL PRACTICE."

THE COMMITTEE WENT ON TO REQUEST A REPORT ON OUR PLANS FOR DEALING WITH THIS SHORTAGE OF PHYSICIANS IN RESEARCH.

EVEN WITHOUT CONGRESSIONAL PRODDING, NIH HAS DEVOTED CONSIDERABLE ATTENTION TO THIS PROBLEM AND HAS UNDER CONSIDERATION SOME MAJOR STEPS TOWARD ITS SOLUTION.

IN THE PORTION OF THE CONGRESSIONAL REPORT PRECEDING THE STATEMENT ON CLINICAL RESEARCH, THE COMMITTEE EXPLAINED ITS DECISION TO INCREASE THE APPROPRIATION REQUESTED FOR ALL RESEARCH TRAINING PROGRAMS BY OVER $18 MILLION IN FY 1983 TO PROVIDE FOR A TOTAL OF 10,000 TRAINEES--A LEVEL PERCEIVED BY THE COMMITTEE AS BARELY LARGE ENOUGH TO BALANCE INEVITABLE ATTRITION FROM ACTIVE PARTICIPATION IN RESEARCH.

THE NIH HAS ALREADY TAKEN SOME STEPS TO ALLEVIATE THE SHORTAGE OF PHYSICIAN-INVESTIGATORS AND IS CONSIDERING OTHERS.

AT THE UNDERGRADUATE MEDICAL STUDENT LEVEL, WE HAVE CONTINUED TO GIVE THE MEDICAL SCIENTIST TRAINING PROGRAMS TOP PRIORITY IN OUR TRAINING PORTFOLIO.

IN THE MSTP PROGRAM THIS YEAR, WE WILL SUPPORT ABOUT 650 STUDENTS MOVING TOWARD A COMBINED MD/PHD DEGREE. WE REGARD THIS PROGRAM AS ONE OF OUR MOST SUCCESSFUL IN TERMS OF BUILDING UP CLINICAL RESEARCH. AN INFORMAL SURVEY OF 66 GRADUATES OF THE PROGRAM FROM THREE SCHOOLS FOUND THAT ONE-THIRD HAD GONE TO BASIC RESEARCH DEPARTMENTS, AND TWO-THIRDS WERE IN CLINICAL DEPARTMENTS. OF THOSE IN CLINICAL DEPARTMENTS, HALF WERE ENGAGED IN CLINICAL RESEARCH WITH HUMAN SUBJECTS.

THE NIH HAS A NUMBER OF PROGRAMS THAT PROVIDE EARLY EXPOSURE TO RESEARCH CAREERS. THIS PAST YEAR OVER 900 MEDICAL STUDENTS AVAILED THEMSELVES OF OFF-QUARTER TRAINING OPPORTUNITIES SUPPORTED BY NIH. WITH THE NEW EXEMPTION OF THE FIRST YEAR OF NRSA SUPPORT FROM PAYBACK OBLIGATION, THE NIH CAN NOW REINSTITUTE THE POST-SOPHOMORE FELLOWSHIP OR ITS EQUIVALENT, AND THUS PROVIDE A FULL YEAR OF RESEARCH TRAINING WITHIN THE MEDICAL SCHOOL EXPERIENCE UNDER AN NIH FELLOWSHIP OR TRAINEESHIP. THE NIH ALSO OFFERS SUMMER RESEARCH FELLOWSHIPS AT BETHESDA, AND DURING THIS PAST YEAR ABOUT 50 MEDICAL STUDENTS PARTICIPATED IN THAT PROGRAM.

IN ORDER TO MAXIMIZE THE OPPORTUNITIES FOR YOUNG PHYSICIANS TO SECURE RESEARCH TRAINING, THE NIH HAS SENT NOTICES TO APPROPRIATE REVIEW BODIES TO GIVE M.D. APPLICANTS SPECIAL CONSIDERATION IN THE AWARD OF RESEARCH FELLOWSHIPS, AND HAS ADVISED DIRECTORS OF CLINICAL RESEARCH TRAINING PROGRAMS TO GIVE SPECIAL CONSIDERATION TO M.D. APPLICANTS BEFORE APPOINTING PH.D. TRAINEES TO THE AVAILABLE SLOTS. NIH IS CONSIDERING OTHER MEASURES AS WELL. THE DISPARITY OF STIPEND BETWEEN RESIDENCY AND FELLOWSHIP REMAINS A SERIOUS PROBLEM. WE ARE PRESENTLY DISCUSSING POSSIBLE MECHANISMS FOR CLOSING THIS FINANCIAL GAP, BUT ADJUSTMENTS ADEQUATE TO ACHIEVE THIS GOAL WILL PROBABLY REQUIRE CONGRESSIONAL APPROVAL AND TAKE TIME.

WE ARE CONSIDERING A NEW TYPE OF TRAINING PROGRAM, PERHAPS CALLED A PHYSICIAN-SCIENTIST TRAINING PROGRAM, WHICH WOULD PROVIDE SUPPORT FOR THREE OR MORE YEARS OF FULL-TIME RESEARCH TRAINING WITH A STIPEND THAT MATCHES RESIDENCY LEVEL. THESE TRAINING PROGRAMS WOULD BE BASED IN DEPARTMENTS WITH ESTABLISHED RECORDS IN PRODUCING PHYSICIAN-SCIENTISTS. THIS PROGRAM WOULD NOT REPLACE CURRENT TRAINING OR FELLOWSHIP PROGRAMS AND WOULD BE SMALLER IN SCALE, PERHAPS LEVELING OFF AT ABOUT 400 TRAINEES IN THREE YEARS. THE GOAL WOULD BE TO RAISE THE TOTAL NUMBER OF M.D. TRAINEES FROM THE PRESENT LEVEL OF 1,900 TO ABOUT 2,300 PER YEAR.

OF COURSE, IN ORDER TO BE ATTRACTED INTO A CAREER IN RESEARCH, THE NEW OR WOULD-BE INVESTIGATOR NEEDS TO KNOW THAT THERE IS A FULL CAREER OPEN IN RESEARCH. WE HAVE TO MAKE CLEAR TO MEDICAL STUDENTS AND YOUNG PHYSICIANS THAT, IF THEY CHOOSE A RESEARCH CAREER, THEY WILL HAVE REASONABLE ACCESS TO PROGRAMS OF SUPPORT FOR TRAINING AND RESEARCH CAREER DEVELOPMENT. THEY CAN THEN EXPECT TO BE REASONABLY SUCCESSFUL AT OBTAINING LONG-TERM STABLE SUPPORT FOR INDEPENDENT RESEARCH, IF THEY DEMONSTRATE ABILITY AND PRODUCTIVITY.

IT HAS BEEN A GOAL OF NIH, THE ADMINISTRATION, AND THE CONGRESS TO ATTEMPT TO STABILIZE SUPPORT FOR RESEARCH AND RESEARCH TRAINING. THIS APPROACH ARISES FROM WIDESPREAD CONCERN THAT MANY POTENTIAL SCIENTISTS WILL NEITHER UNDERTAKE NOR PERSIST IN A RESEARCH CAREER IF SUBSTANTIAL YEARLY FLUCTUATIONS OCCUR IN THE NUMBERS OF AVAILABLE GRANTS. THE GOAL HAS BEEN TO STABILIZE RESEARCH BY AWARDING, AT A MINIMUM, ABOUT 5,000 COMPETING INVESTIGATOR-INITIATED RESEARCH PROJECT GRANTS PER YEAR. MORE THAN HALF OF THIS NUMBER REPRESENT NEW PROJECT GRANTS EACH YEAR, AND ABOUT HALF OF THESE ARE MADE TO FIRST-TIME PRINCIPAL INVESTIGATORS. IN 1982, TEN PERCENT OF ALL RESEARCH PROJECT GRANTS WENT TO FIRST-TIME PRINCIPAL INVESTIGATORS. AND THIS FIGURE IS TYPICAL OF THE LAST DECADE!

I HOPE THAT YOUNG PEOPLE WILL BE CONVINCED OF THE EXCITEMENT OF CLINICAL RESEARCH, THE IMPORTANCE OF ADEQUATE TRAINING AS A BASIS FOR THEIR CAREERS IN RESEARCH, AND AVAILABILITY OF PROGRAMS TO ENSURE THEIR NECESSARY TRAINING AND SUBSEQUENT SUPPORT. WE HAVE AN ETHICAL IMPERATIVE TO WED THE LABORATORY AND THE CLINIC; ONLY THE CLINICAL INVESTIGATOR CAN DO THIS. NIH WILL CONTINUE TO SAFEGUARD THE ATTRACTION AND RETENTION OF PHYSICIAN-SCIENTISTS FOR THE BIOMEDICAL RESEARCH ENTERPRISE.

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[1]Statement of Dr. George Keyworth, Director, Office of Science and Technology Policy, Executive Office of the President, before the Committee on Science and Technology, U.S. House of Representatives, December 10, 1981.

[2]John W. Gardner, "Excellence: Can We Be Equal and Excellent Too?" Harper & Row, Publishers, New York and Evanston, 1961.

[3]NIH Program Evaluation Report: On the Status of Medical School Faculty and Clinical Research Manpower 1968-1990, NIH Publication No. 82-2458, "A Report to the Clinical Sciences Panel of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel," National Academy of Sciences, National Research Council, April 30, 1981.

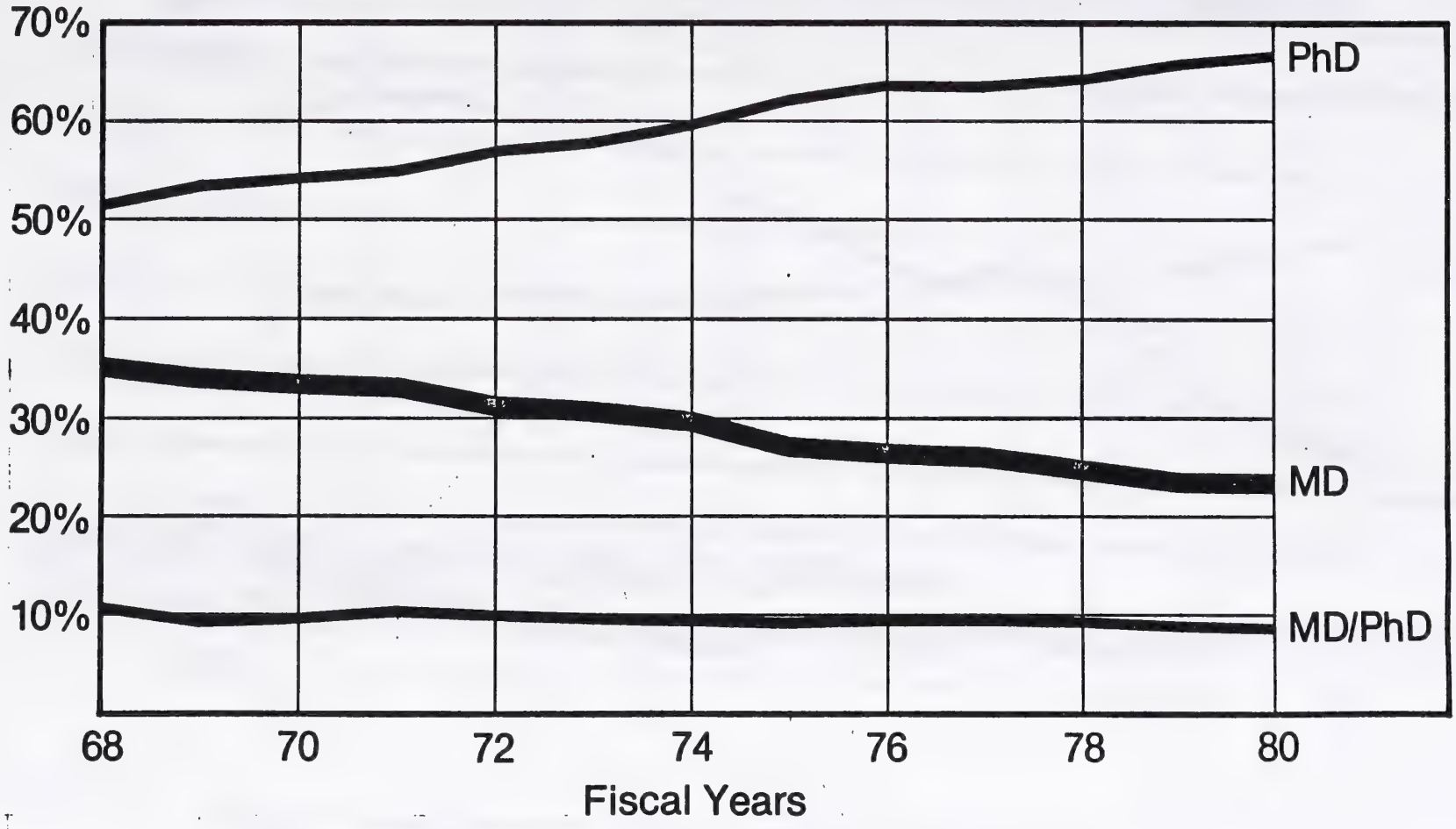
[4]Charles R. Sherman, Ph.D., and George Bowden, "Updated Trends and Some New Observations About Medical School Faculties," Office of Program Planning and Evaluation, NIH, October 1982.

[5]Janet Cuca, "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapproval," Division of Research Grants, NIH, September 1982.

[6]Report No. 97-894, 97th Congress, 2nd Session, House of Representatives, "Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 1983," September 29, 1982.

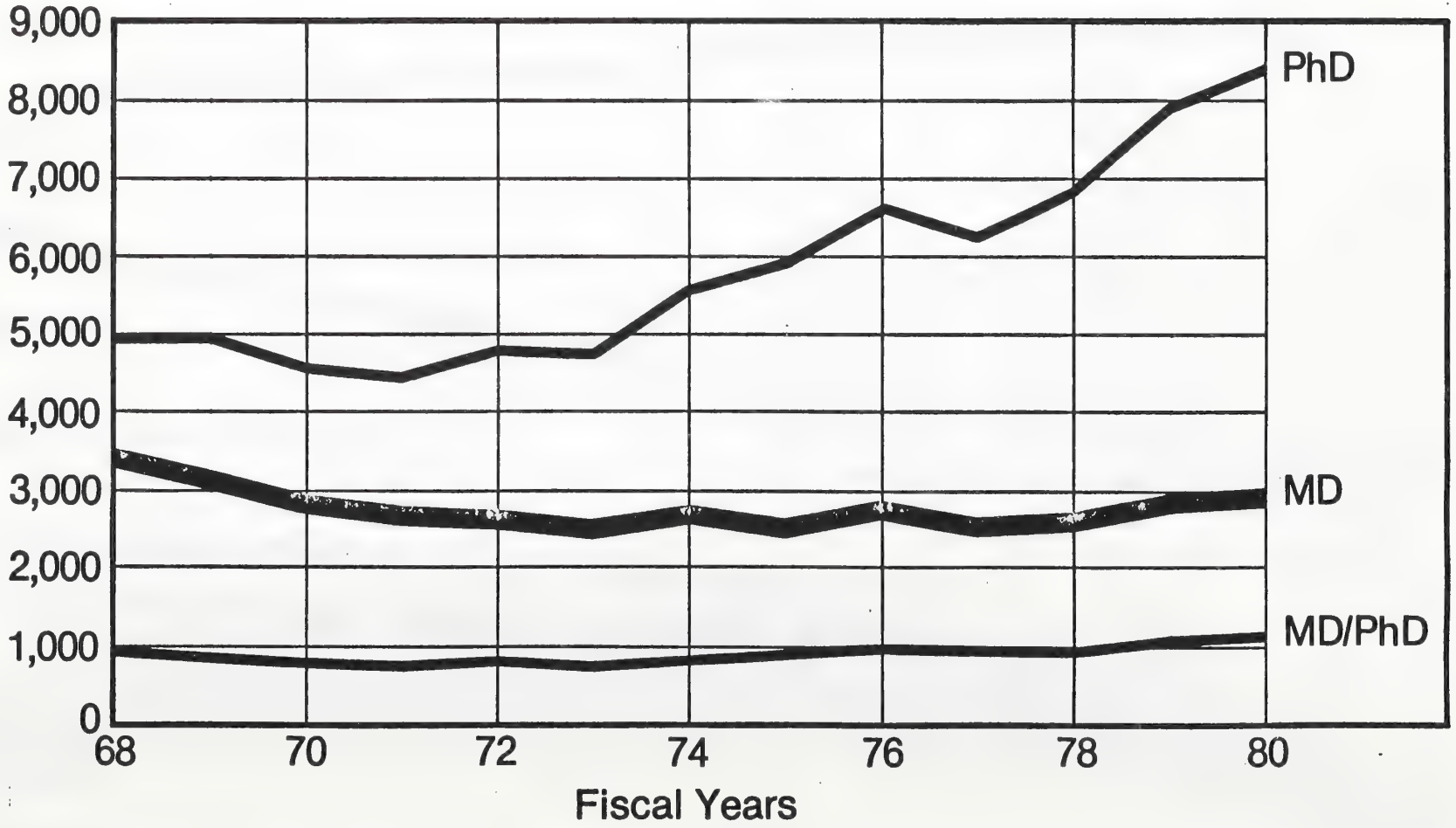
SLIDE

P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants



SLIDE 2

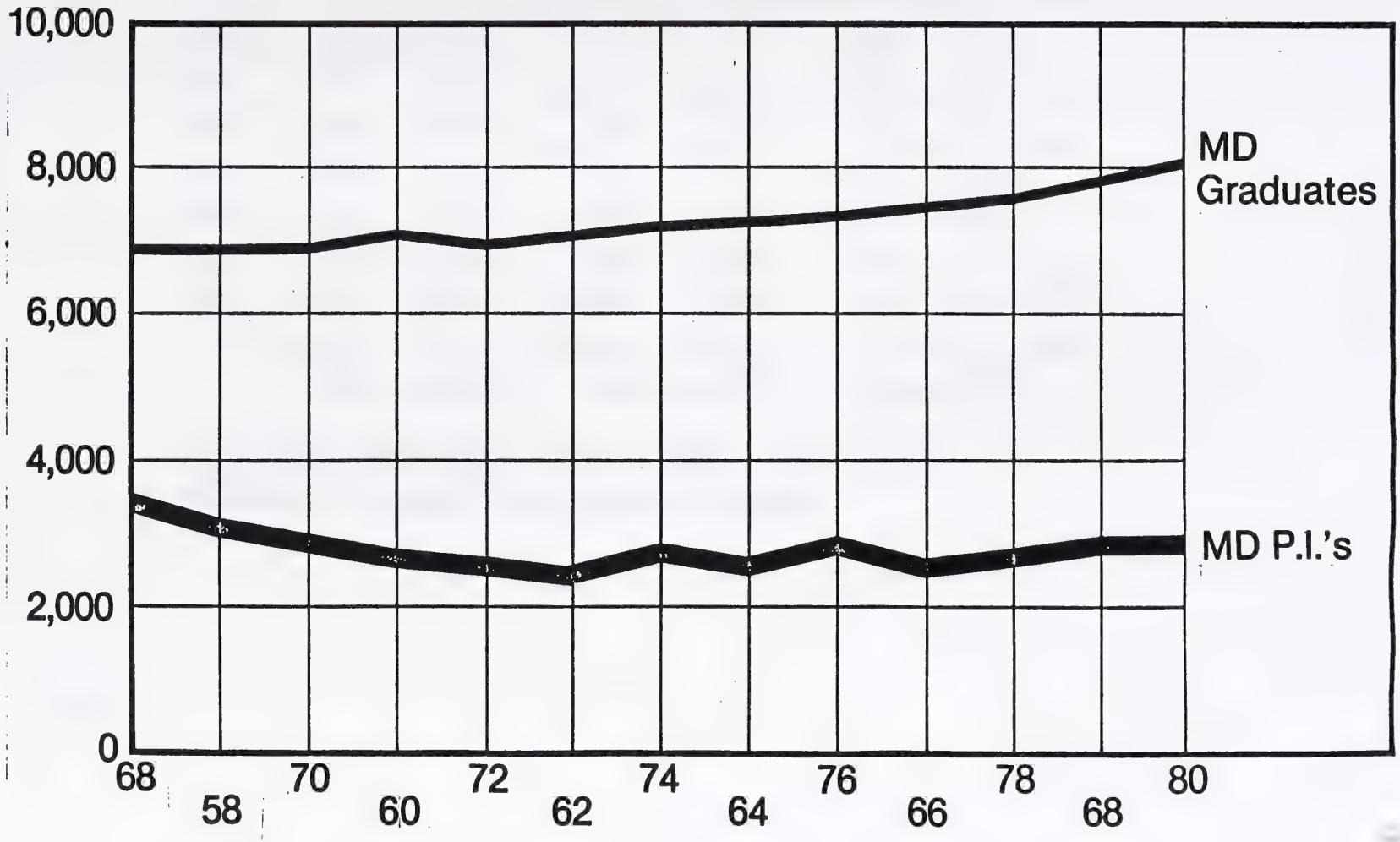
Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



SLIDE 3

Number of MD P.I.'s on All R01 Grants Compared with Number of MD's who Graduated Eleven Years Previously

(Average Interval of 11 Years between Medical School Graduation and Beginning of First Grant per Douglass and James [Science 7/20/73])



SLIDE 4

Approval, Award, and Success Rates for Competing R01 Applications: 1974-1980

	Approval Rate (%)		Award Rate (%)		Success Rate (%)	
FY	M.D.	Ph.D.	M.D.	Ph.D.	M.D.	Ph.D.
1974	73.9	78.9	60.7	56.0	44.3	44.2
1975	72.0	77.4	59.5	60.2	42.8	46.6
1976	67.7	73.8	50.4	47.2	34.1	34.8
1977	72.0	76.0	41.2	36.8	29.7	28.0
1978	74.4	80.2	44.1	45.5	32.8	36.5
1979	76.1	79.4	51.1	51.7	38.9	41.1
1980	76.7	81.0	41.5	41.7	31.9	33.8

SLIDE 6

Competing R01 Applications 1976-1981

	Number Reviewed	Recommended	Award Rate	Success Rate
No Human Subjects:				
— M.D.	10,552	73%	42%	31%
— Ph.D.	40,815	74%	40%	30%
Human Subjects:				
— M.D.	12,166	64%	39%	25%
— Ph.D.	12,078	61%	38%	23%

Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - Hypothesis (47%)
  - Significance (30%)
- Experimental Design:
  - Study Group or Controls (40%)
  - Technical Methodology (66%)
  - Data Collection Procedures (41%)
  - Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

Average Success Rates on NIH Competing Research Grant Applications

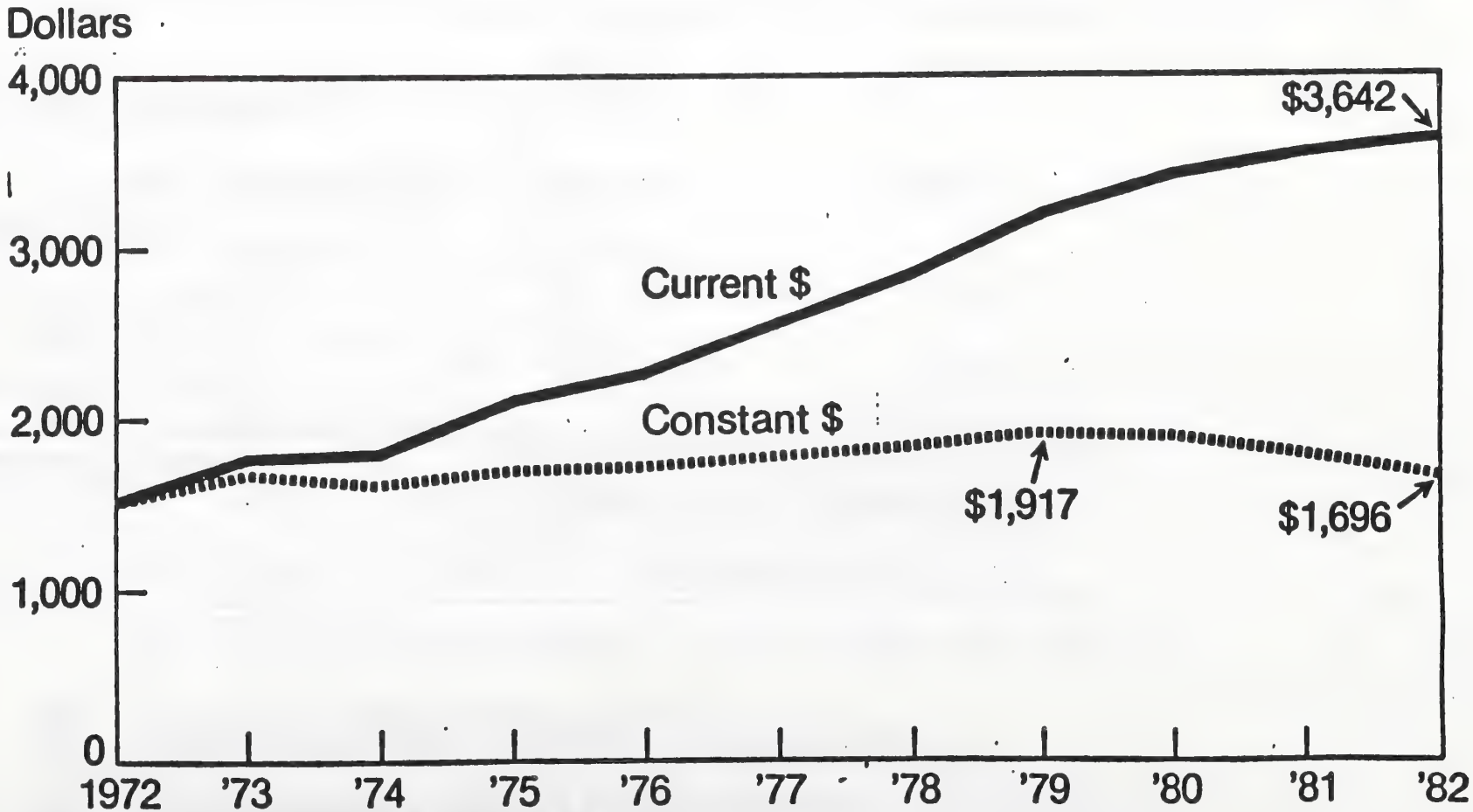
By Doctoral Degree and NIH/PHS Training Support*
Fiscal Years 1967-1978

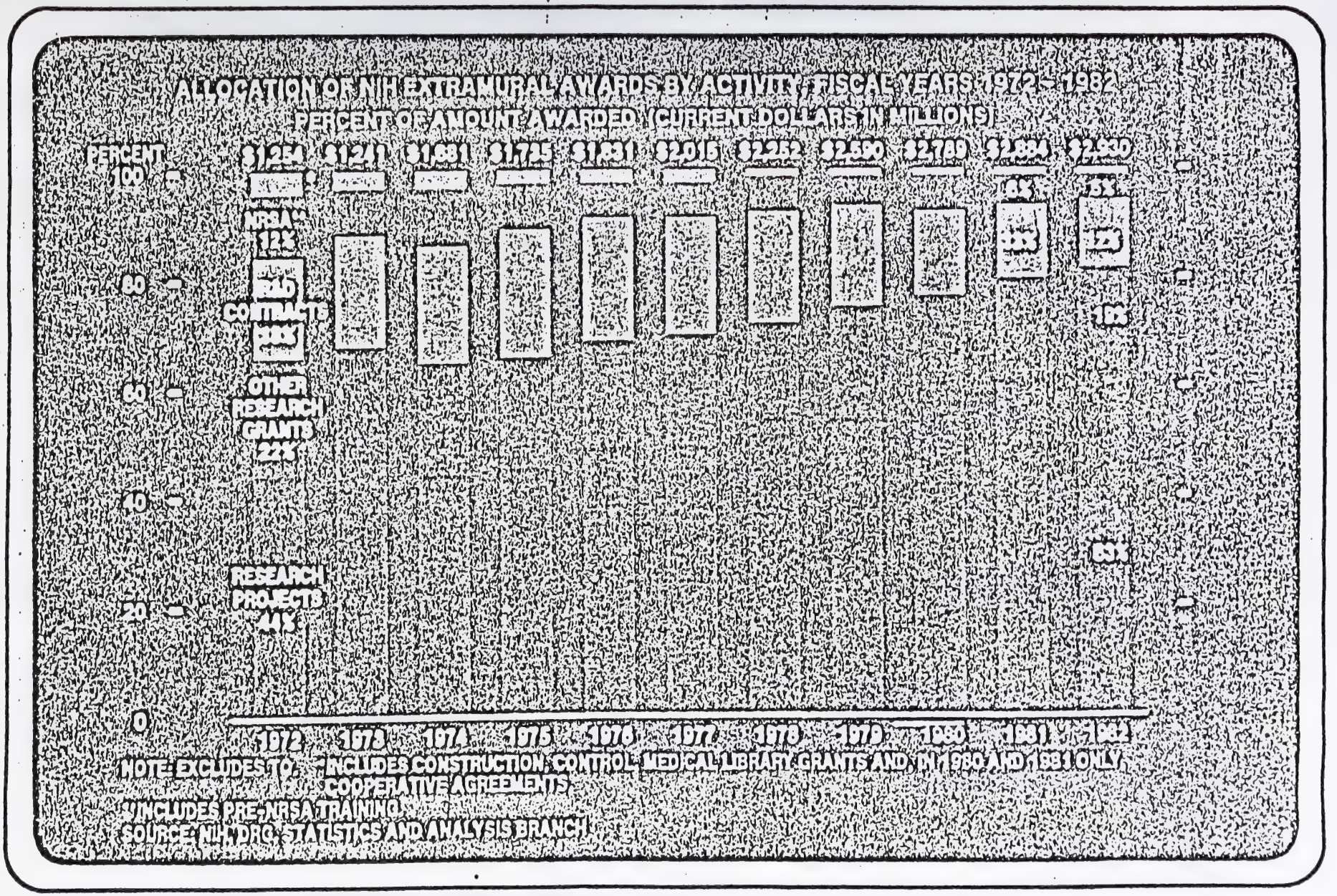
Doctoral Degree	Success Rates	
	With Training Support	Without Training Support
M.D. or Equivalent	36.5%	25.0%
Ph.D. or Equivalent	37.9%	27.1%
Professional & Academic (e.g., M.D./Ph.D.)	40.4%	29.4%
Other Professional Doctorates	41.7%	27.6%

*Based on five percent random sample of NIH Grant Applicant Summary File, which includes R, P, M, and S grants. Success rate is the ratio of funded competing research grant applications to all such applications multiplied by 100. Source: DPA/OPPE/OD/NIH.

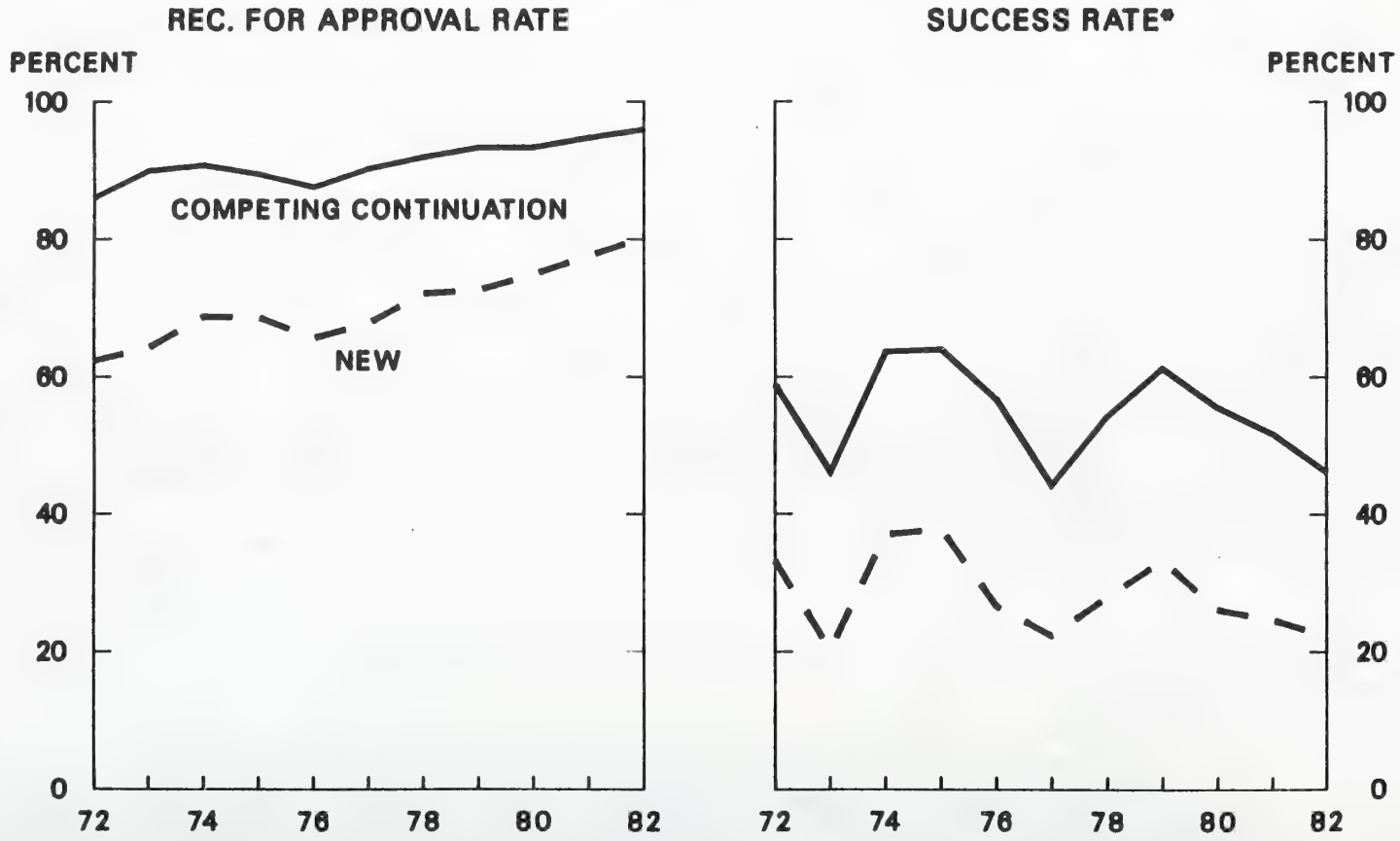
Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)



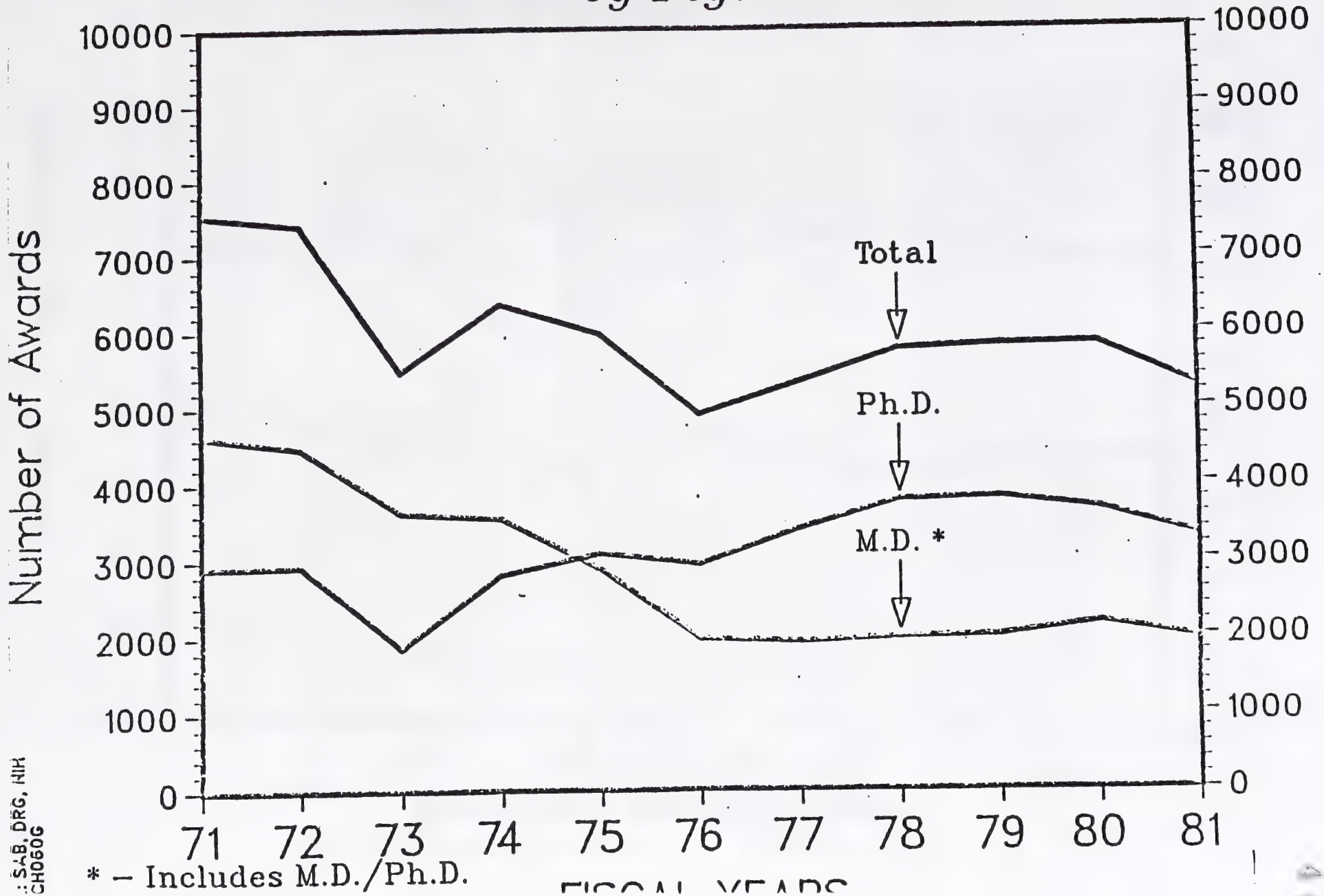

ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972 - 1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)
PERCENT
100
80
60
40
20
0
$1254
$1241
$1681
$1715
$1931
$2015
$2252
$2590
$2740
$2884
$2930
NRSA 12%
RESEARCH CONTRACTS 10%
OTHER RESEARCH GRANTS 22%
RESEARCH PROJECTS 41%
6%
5%
12%
10%
6%
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
NOTE: EXCLUDES (1) INCLUDES CONSTRUCTION, CONTROL, MEDICAL LIBRARY GRANTS AND (2) 1980 AND 1981 ONLY
COOPERATIVE AGREEMENTS
INCLUDES PRE-NRSA TRAINING
SOURCE: NIH/DRG STATISTICS AND ANALYSIS BRANCH

COUNCIL RECOMMENDED FOR APPROVAL AND SUCCESS RATES FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS BY TYPE, FISCAL YEAR 1972-1982



NOTE: DATA BASED ON NIH STANDARD PROCEDURES.
*AWARDS AS A PERCENT OF REVIEWED INCLUDING FUNDED CARRY-OVERS.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

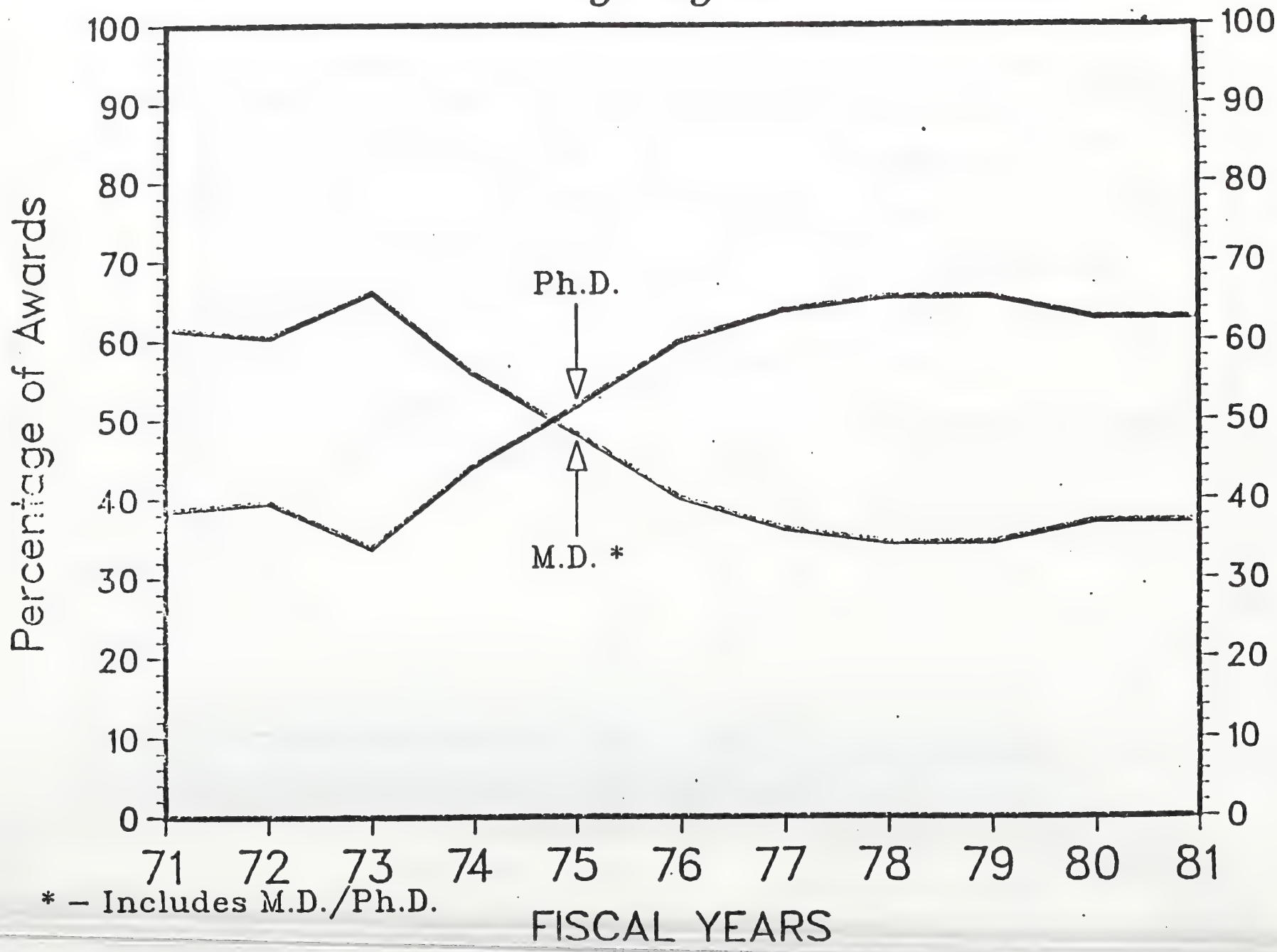
Numbers of N. I. Postdoctoral Trainees and Fellows by Degree



* – Includes M.D./Ph.D.

SAB, DRG, NIH
CH060G

Percentage of [illegible] Postdoctoral Trainees and Fellows by Degree



PROGRAM AND POLICY DIRECTIONS OF THE NATIONAL INSTITUTES OF HEALTH*

by

James B. Wyngaarden, M.D.**

I am pleased to be able to discuss program and policy directions of the National Institutes of Health with members of the Council of Academic Societies and your Congressional and Departmental guests this afternoon. The AAMC and the CAS represent the scientific faculties who are the original members of the federal-academic partnership in biomedical research that has functioned so effectively since the 1940s. There are a number of serious problems in the conduct and support of biomedical research that we will need to address in a collegial manner. We are very much together in this effort, as a few statistics will indicate.

The federal government supports an estimated 90 percent of basic biomedical research in this country and more than 60 percent of research and development at American universities and medical schools is funded by NIH. Extramural awards in Fiscal Year 1982 accounted for 81 percent of the NIH budget of $3.6 billion (slide 1) and 52 percent of awards went to medical schools (slide 2).

I welcome, as your letter of invitation said, this "dialogue regarding how we can better work together to maintain the viability of academic health centers and their commitment to research and education." Each step in the growth of our research enterprise has been in response to a unique set of circumstances created by the evolution of science, technological developments, the changing expectations and priorities of the public as expressed by the Administration and Congress, and by economic conditions. Most recently it has been the combination of economic conditions and changing public perception that has had the greatest influence on our activities.

BUDGET

A look at how our budget has changed during the last 25 years is instructive in that regard. NIH's main program growth came during the decade 1955-1965, with appropriations growing roughly fourteenfold. Slide 3 shows the NIH budget in both current and constant dollars from 1972 to 1982. Between 1972 and 1982, there has been a 15 percent increase in constant dollars, but the growth of indirect costs during this period has almost exactly consumed this increment so that the funds available to support the direct costs of research are essentially the same in 1983 as in 1972. Our peak year was actually in 1979. The budget fell by 12 percent in purchasing power between 1979 and 1982

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*Remarks at the 1983 Interim Meeting of the Council of Academic Societies, Washington Hilton Hotel, Washington, D.C., February 14, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

and rose by 4 percent in 1983 for a net decrease of 8 percent. The Fiscal Year 1984 budget for NIH submitted to Congress by the President requests $4.077 billion. That would be a $73 million, or 1.8 percent, increase over Fiscal Year 1983, for which an inflationary rate of 5 percent is predicted.

In short, the NIH budget has been essentially in a steady state for more than a decade, and we cannot expect dramatic increases in the near future, certainly not until the national economy improves. At the same time, biomedical research has received strong support from present and previous administrations and congresses, and the NIH has fared better than many other agencies in recent years. The importance of the national investment in biomedical research to public health is widely recognized.

Historically we have been accommodating to a relatively constant budget and an increasing number of excellent research proposals by shifting funds among mechanisms. These changes began in 1975 (slide 4) but were not articulated as a policy until Fiscal Year 1980 when we asked the Congress for sufficient funds to support a minimum of 5,000 new and competing research grants and 10,000 trainees.

POLICY AND PROGRAM ISSUES

With that context in mind, I would like to consider some program and policy issues that face NIH and our partnership. Steady-state resources inevitably intensify competition for support in all areas for which NIH is responsible. In addition to extramural research project grants, these include centers, contracts, clinical trials, research instruments, and facilities, as well as the intramural programs and facilities at NIH. Since our fundamental mission is the improvement of health and well-being, we must also emphasize prevention of disease and disability and make a special effort to see that scientific discoveries are transferred to medical practice as quickly as appropriate.

In awareness of those multiple responsibilities and of fiscal constraints, we have placed the highest priority on these objectives:

- To sustain maximum stability in the investigator-initiated research project base.
- To support the training of an optimum number of new investigators to assure continuity of high-quality research in the future.
- To organize the agency for maximum efficiency in support of modern biomedical research.

STABILIZATION OF RESEARCH GRANTS

We continue to emphasize stability in the research project base because pursuit of fundamental knowledge is the foundation of progress in the health sciences and investigator-initiated research holds the greatest promise of significant discovery. Our objective is to provide a steady and predictable level of research project support, one that offers continuity to established investigators and their work, and that encourages new scientists to enter the field.

The stabilization policy has in fact done just that. We have been able to dampen large fluctuations in support of new and competing renewal awards. In 1981, we supported 5,140 grants, and in 1982, 5,027 grants.

The 1983 budget will enable us to support some 4,914 new and competing renewal grant awards out of a research grant portfolio of about 16,357. We are also supporting some 9,969 trainees. To achieve that level, however, we have had to shift funds from some mechanisms, most notably clinical trials and initiatives to emphasize special areas or activities, such as research centers. The Fiscal Year 1984 budget is still being negotiated with OMB. Without additional budgetary shifts, the President's budget would support 3,676 competing awards and 9,105 trainees.

The difficulty of setting priorities among competing demands can be illustrated by examining the changing level of support in various mechanism categories over the past decade.

Given finite resources and a commitment to stability in one growing element among several necessary activities, the ultimate result is de-stabilization of the others. In fact (slide 5), if the current rate of increase in percent of NIH budget devoted to the extramural grant component were to continue, it would reach 100 percent around 1993.

Those pressures will intensify in the future because of some trends over which we have little or no control. For example, the average cost per grant has grown faster than the rate of inflation, and indirect costs have increased faster than direct costs: (Slide 6) Between 1972 and 1982, direct costs increased by a factor of 3.6 and indirect costs rose almost fivefold. The clearest reflection of this differential occurred in Fiscal Year 1982. Of $52 million additional provided by the Congress for extramural research, $29.1 million, or 55 percent, went to indirect costs.

The dilemma is: How are we to ensure that all essential and vital activities are continued while stability in the research and training base is maintained? Many Institute directors feel that further shifts would seriously limit their ability to meet other program goals and to maintain program balance. This year we are involving the Director's Advisory Committee in a review of the impact of our stabilization policy on all of NIH and particularly on the extramural program. We will also analyze the factors contributing to the increasing cost of research projects, including an analysis of indirect costs and of faculty salary support, with a view toward achieving greater efficiency in the support of research. But I am convinced that, even after careful review, the concept of stabilization will be reaffirmed as a policy.

The academic community might also explore ways in which we could both reduce overhead costs in the preparation and review of grant applications. Between 1981 and 1982, for example, the number of competing applications rose from 15,732 to 16,989, the latter total almost double the 8,600 applications received in 1972. Last year, 25 percent of all applications were re-submissions. This figure is twice the number of 3-5 years ago. Additionally there appears to be a trend toward multiple applications per investigator and a flooding of the

market by some schools. A large number of submissions does not necessarily correlate with an increased number of awards. In fact, in a review of applications from major research-oriented medical schools in 1981, we found that the university whose faculty submitted the least number of applications (155) was awarded the largest number of grants (83). While we do not suggest that there be any restriction on good ideas, we do suggest that a greater measure of quality control in preparation and submission of grant applications at the institutional level could save time and expense for the faculty, the Division of Research Grants, and study section reviewers.

Training

Another continuing issue of concern is the training of sufficient numbers of investigators to maintain the vitality of research. There are considerations beyond numbers. For example, although there currently is an adequate supply of scientists in most fields, a diminishing proportion of physicians is engaging in NIH supported research (SLIDE 7). The success rate among applicants for grants is greatest for investigators with combined M.D./Ph.D. degrees, followed by Ph.D.s, with M.D.s last (SLIDE 8).

There are also fewer physicians interested in training themselves as researchers. Of the 2,800 positions that the National Academy of Sciences recommends be devoted to clinical training, approximately 900 are now filled by Ph.D.s, compared with only 450 several years ago. The major barriers to attracting M.D.s appear to be the perception of instability in support for research, the increasing complexity of science which in turn leads to a need for longer training, the widening gap between laboratory and bedside, the debt load incurred by physicians, and the stipend which averages some $6,000 less than an equivalent house staff position in a hospital. The solutions are also complex, including earlier exposure of students to research experiences; greater flexibility in medical curricula, graduate training and board requirements, a realization among researchers and trainees that a substantial period of training is required, higher stipends for post-M.D. trainees, and an assurance by Federal agencies of both stability and access to the system by young investigators.

An increase in the physician's stipend might attract M.D.s into research training but, given a limited budget, this would force a reduction in number of trainees. We need to maintain the support level for non-clinical training while finding incentives to encourage more physicians to enter research.

To this end we are considering a new type of training program, perhaps called a Physician-Scientist Training Program, which would provide support for three years of full-time research training with a stipend that matches residency level. These training programs would be based in departments with established records in producing physician-scientists. This program would not replace current training or fellowship programs and would be smaller in scale, perhaps leveling off at about 400 trainees in three years. The goal would be to raise the total number of M.D. trainees from the present level of 1900 to about 2300 per year.

Organization

Another priority concern is to preserve the ability of the NIH to accommodate to changing demands of biomedical science and to provide the most effective management. With growing public awareness of the potential for successful intervention in disease processes, we can expect continued pressure for additional, narrowly focused research efforts. In recent years, for example, there have been 10 proposals for new Institutes (SLIDE 9) and five proposals to transfer to NIH functions from other Public Health Service agencies (SLIDE 10). In my opinion additional categorical, disease-specific institutes at NIH would not contribute to the most efficient administration of research and would only lead to increased administrative costs at the expense of funding for research. To help resolve questions of NIH organization, we have asked the Institute of Medicine to make an 18-month study of the present structure, to examine its adequacy and efficiency and to devise criteria by which we can evaluate and determine need for future change. I urge you to participate actively in this effort.

Legislative Issues

There are several issues of concern to NIH and the biomedical research community that are likely to be addressed by the 98th Congress. One will be the organization of NIH, and specifically proposals to establish additional Institutes or to transfer agency functions, as I mentioned earlier. Various committees will undoubtedly be seeking your counsel in this matter and I urge you to respond in awareness of the over-all context in which we all are working at this time.

Also, certain to come before Congress in this session is the reauthorization of several NIH programs. Appropriation authority for the Cancer and Heart Institutes and the Medical Library Assistance program of the National Library of Medicine expired at the end of fiscal year 1982. Other programs which will expire at the end of 1983, and will require authorization for operation in fiscal year 1984, include National Research Service Awards and several advisory boards, centers and information programs of the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases. I am concerned about attempts to amend further or revise our statutory authorizations. Section 301 of the Public Health Service Act has been the legislative cornerstone of our research activities for more than 40 years. It provides the continuity consistent with the long-term requirements of fundamental research.

We also expect reintroduction of legislation involving the use of animals in research and testing, about which we will hear more later this afternoon. Many other issues will come before Congress in various connections, such as indirect cost reimbursement, misconduct in science, ethical aspects of genetic engineering, and commercialization of research. All call for careful consideration and response. But we must be wary of the legislative quick fix. There is, of course, a long history of cooperation of NIH and the research community with the Congress. To cite two examples: NIH, working with other PHS agencies, has drafted regulations governing misconduct in science and will issue them shortly. I know you, through the AAMC, have done

the same. Similarly, we are taking steps, such as site visits to selected institutions that use laboratory animals in research, to determine whether institutional assurances reflect actual compliance with NIH guidelines and Federal law.

Conclusion

I have mentioned but a few of the difficult issues we face; there are others, as you are all aware. I include on this list three that are of longer range. Foremost is the need to assure adequate levels of support for the research enterprise. Currently our award rate is 33 percent of approved applications. We believe an optimal level for progress would be 45-50 percent. In the context of the Federal budget the sums needed are not large. To achieve this goal we would need an additional $300-400 million per year for three years, and thereafter an annual budget of $5 billion, adjusted for inflation.

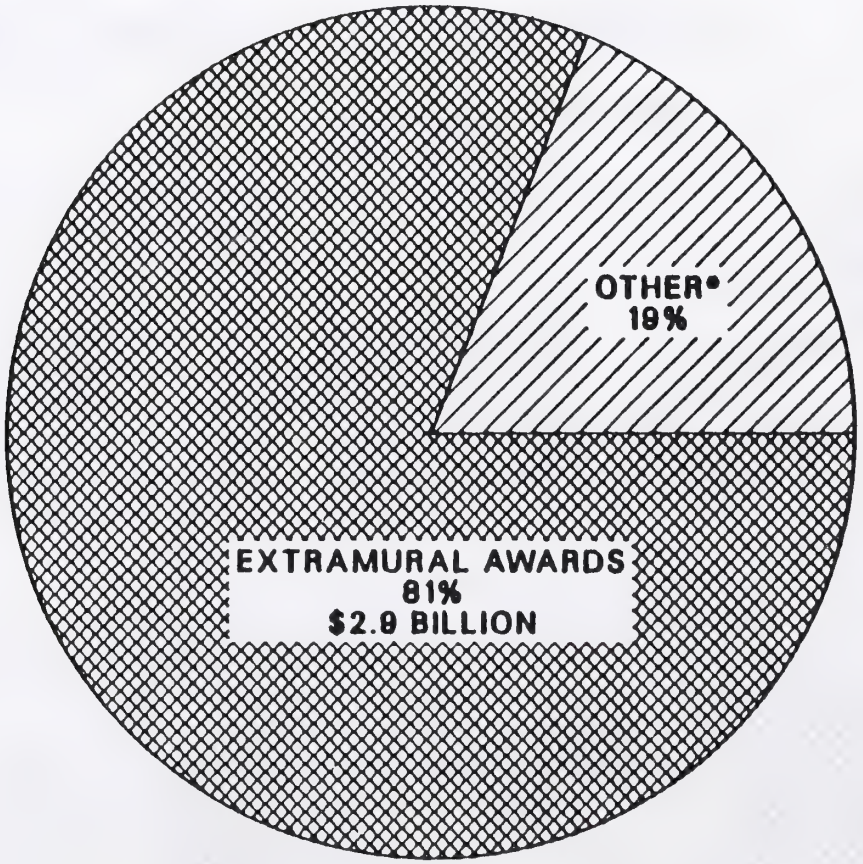
A similar problem exists in replacing or purchasing the increasingly sophisticated research instrumentation our laboratories now require. It is estimated that $20 million a year for five years is needed for the acquisition of large-scale shared-instrumentation resources with additional funds for the purchase via research grants of smaller instruments.

Finally, extramural laboratories and facilities are slowly deteriorating. With the exception of funds supplied by the Cancer program and, more recently, by the Eye Institute, NIH stopped supporting facilities after 1969. We need to help modernize and to construct new laboratories.

I want to emphasize that it is not possible to accomplish these goals in the immediate future. Given the current state of the economy, I believe NIH has fared well. Our budget represents a strong commitment by the Administration to biomedical research. But I also believe that as the economy improves it is imperative to increase that level of support.

Our past history of cooperation in the evolution of the Nation's great biomedical research enterprise gives me confidence in our ability to solve current problems through working together. While we all encourage the intense competition that drives scientific discovery, we should view ourselves as collaborators in operation of the system that supports the research efforts. We are vitally concerned for the health and stability of the institutions in which so much of the essential research is conducted, just as you are for the success of NIH. On behalf of NIH, I invite your advice, counsel and support in the months ahead.

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET
FISCAL YEAR 1982

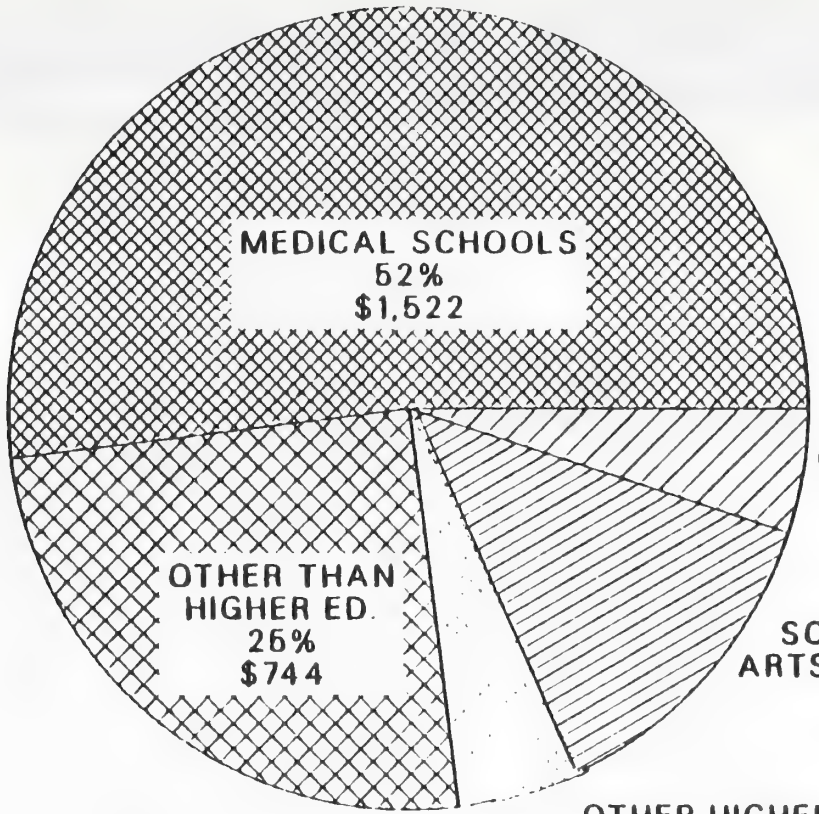


TOTAL - $3.6 BILLION

*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



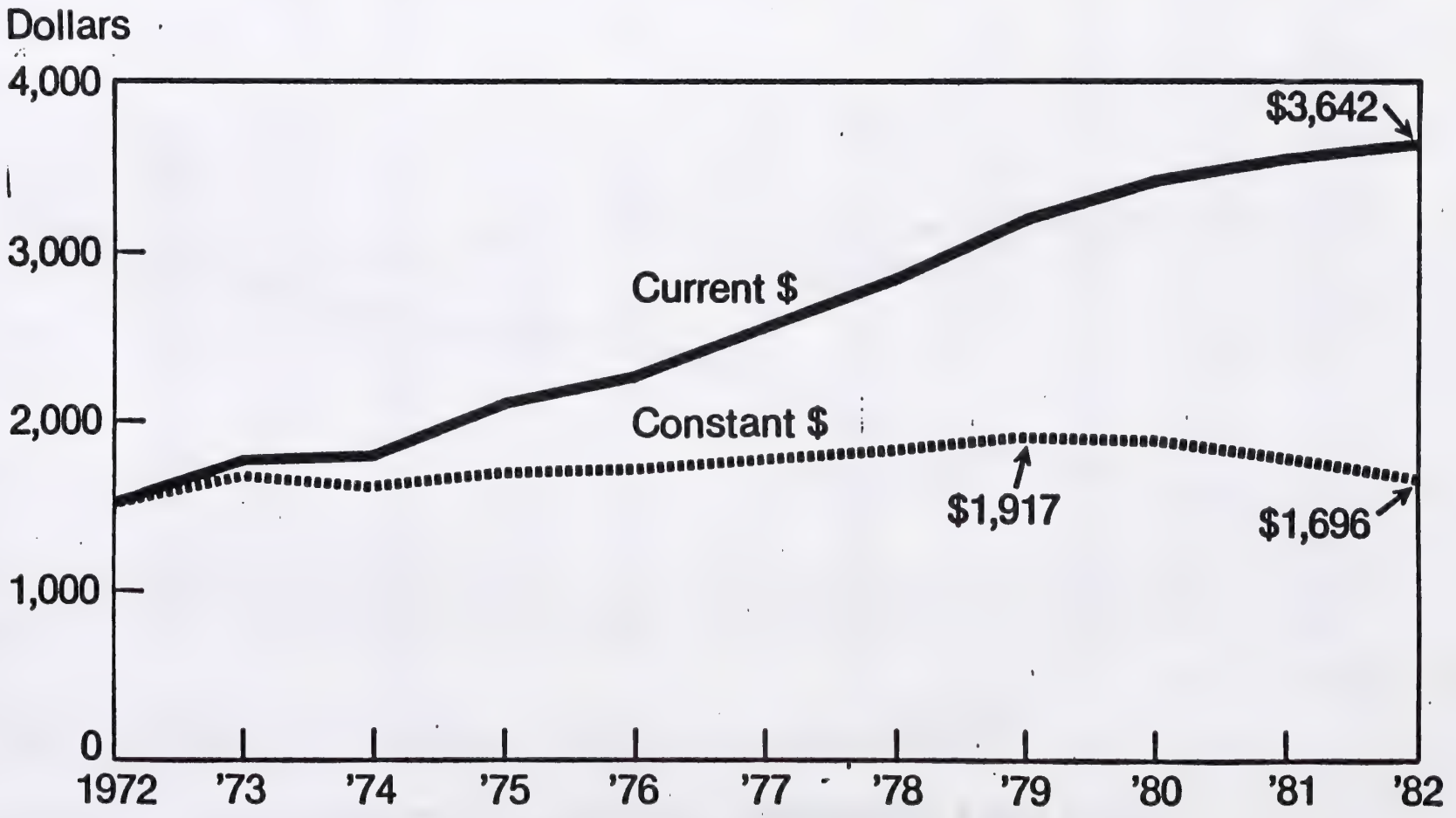
FY 1982*

$2,933 MILLION

*PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

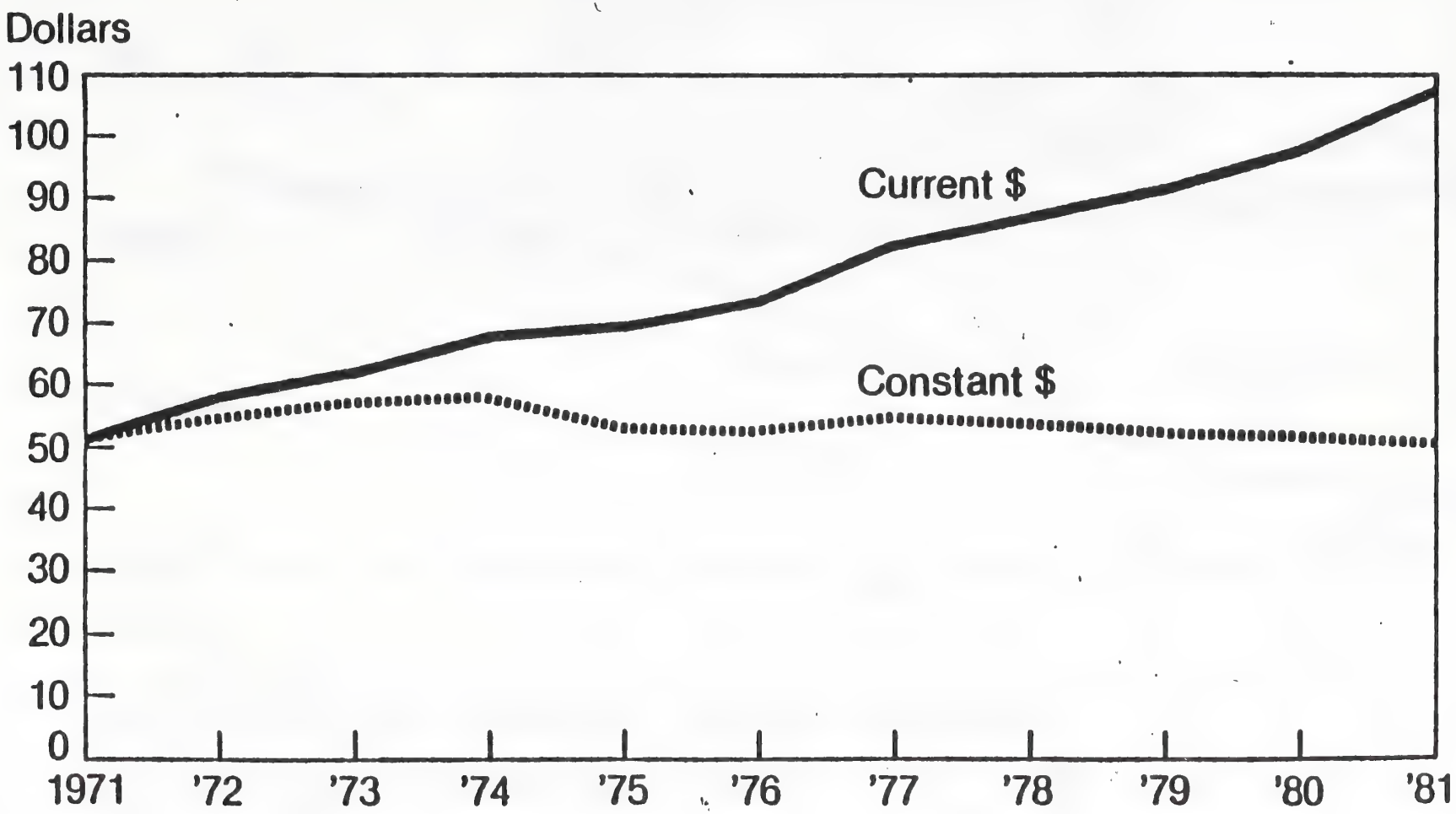
Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)

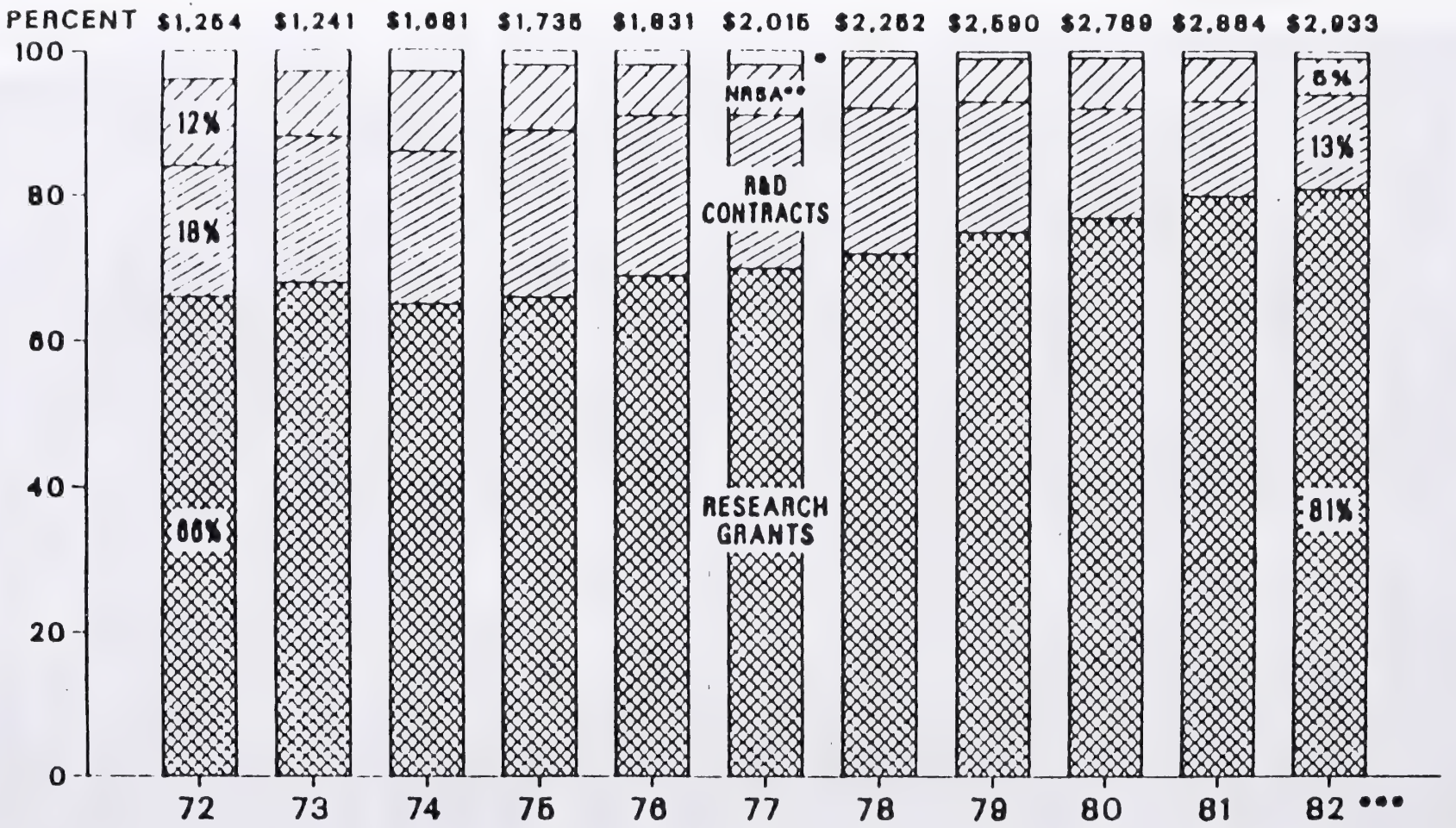


Average Research Project Grant, 1971-81

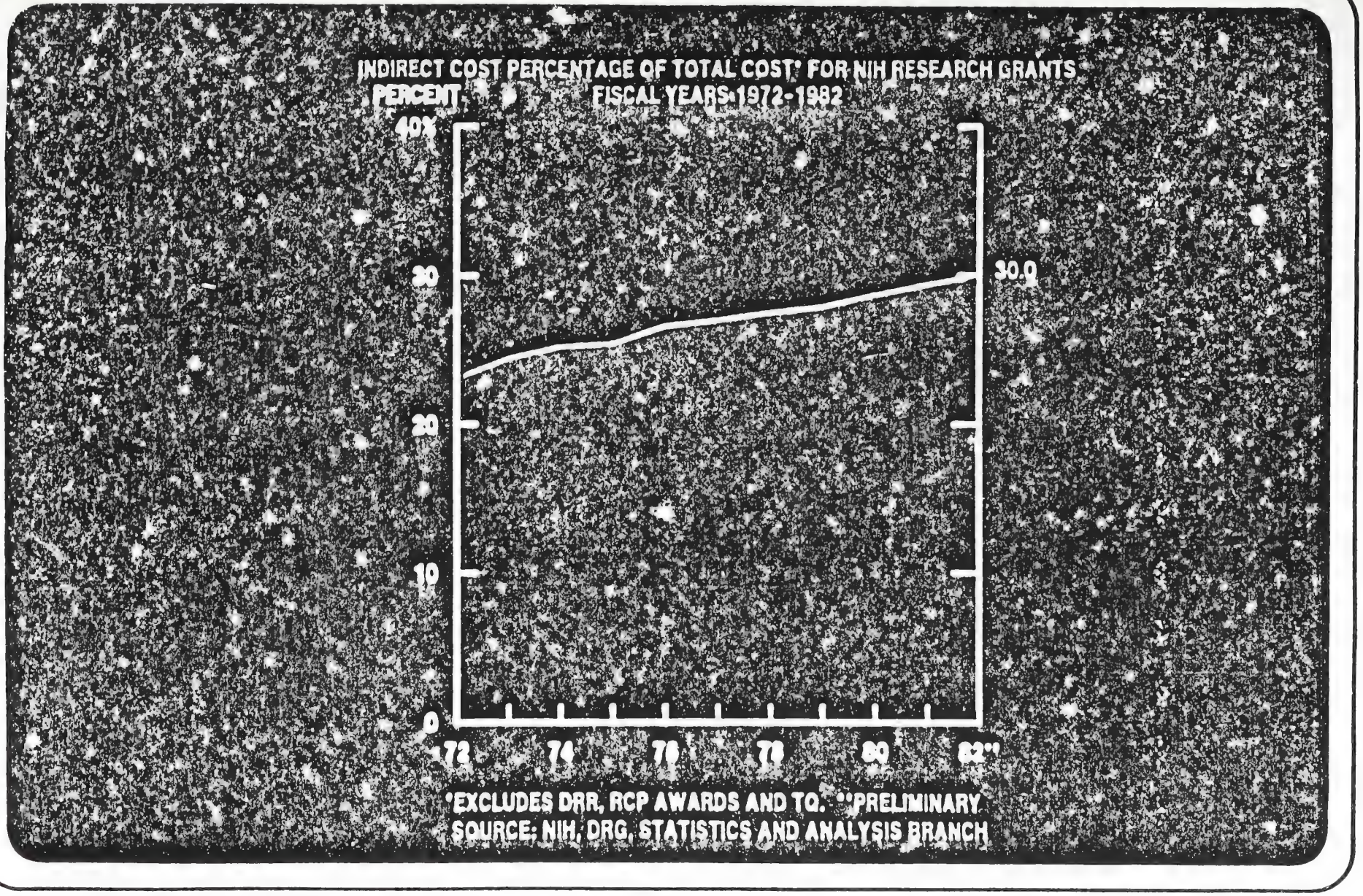
In Current and Constant Dollars (Thousands)



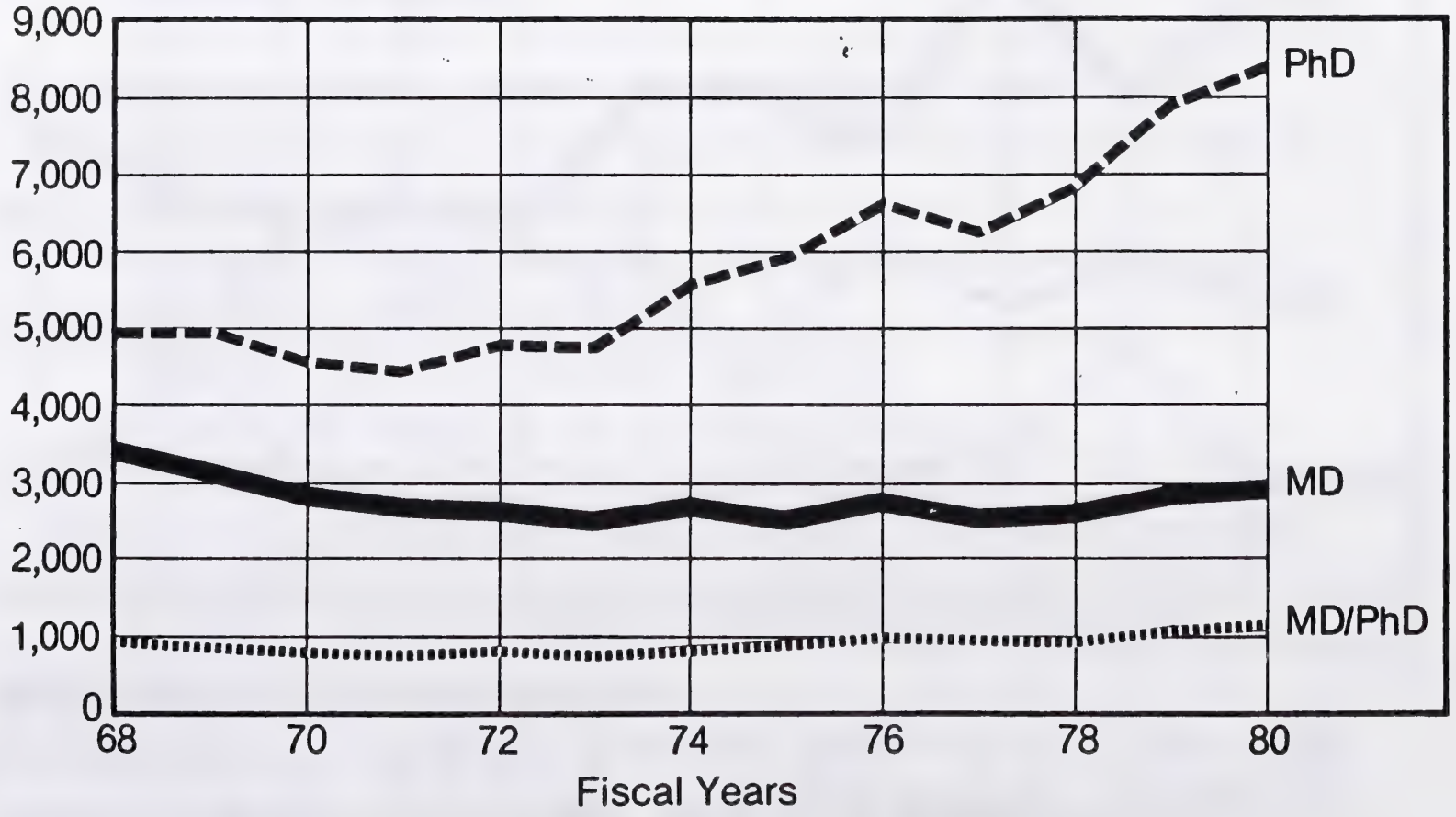
ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



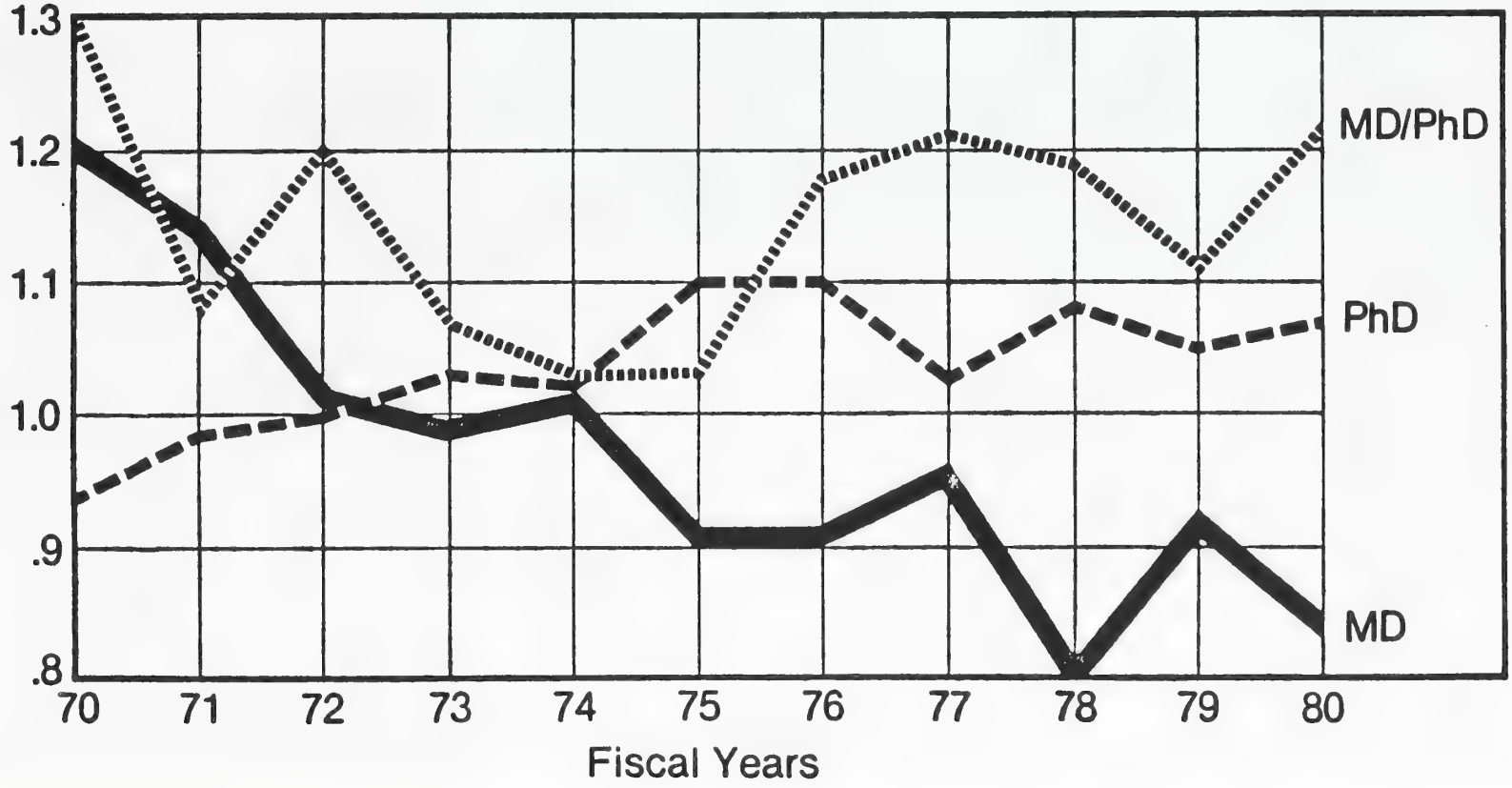
NOTE: EXCLUDES TQ. *INCLUDES CONSTRUCTION, CONTROL, AND MEDICAL LIBRARY GRANTS.
**INCLUDES PRE-NRSA TRAINING. ***PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH


INDIRECT COST PERCENTAGE OF TOTAL COST* FOR NIH RESEARCH GRANTS
PERCENT
FISCAL YEARS 1972-1982
40%
30
20
10
0
30.0
72
74
76
78
80
82**
*EXCLUDES DRR, RCP AWARDS AND TO. **PRELIMINARY
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



Success Rates of New MD, PhD and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year



Unsuccessful Proposals for Major Organizational Change at NIH

Proposed Institutes
National Institute for International Medical Research (L)
National Institute of Emphysema and Respiratory Disease (L)
National Kidney Institute (L)
National Institute of Marine Medicine and Pharmacology (L)
National Lung Institute (L)
National Sickle Cell Anemia Institute (L)
Institute for Research on Dysautonomia (L)
National Institute for Population Research (L)
National Institute of Diabetes, Endocrinology and Metabolic Diseases (L)
National Institute of Arthritis and Musculoskeletal Diseases (L)

L — Proposed Legislatively
A — Proposed Administratively

Unsuccessful Proposals for Major Organizational Change at NIH

PHS Components Proposed for Transfer to NIH

National Institute for Occupational Safety and Health (L)

Alcohol, Drug Abuse and Mental Health Administration (A)

National Center for Health Services Research (L)

National Center for Health Statistics (L)

National Institute of Mental Health (L)

L — Proposed Legislatively
A — Proposed Administratively

INTRODUCTION OF DR. BENJAMIN ALEXANDER

by

James B. Wyngaarden, M.D.*

Black History Month Program**

This year I am having my first opportunity to participate in the annual observance by the NIH of Black History Month. I am told that the programs presented here during the past ten years in celebration of Black History Month have been outstanding. Certainly this is true of the 1983 observance. The Minority Cultural Committee has developed an interesting series of presentations that express in different and effective ways the Black experience and remind us of the richness of the Black heritage in America.

It is my privilege and pleasure to present the principal speaker for today's program, Dr. Benjamin H. Alexander. His appearance is a kind of homecoming for Dr. Alexander, for less than ten years ago he was a member of the NIH community as a health science administrator. After a 20-year career as a research chemist and administrator in the Federal Government, he left the NIH in 1974 to become the president of Chicago State University. His vigorous and capable administration of that institution for eight years brought him national recognition. Last August he accepted the even greater challenge of leading the University of the District of Columbia where his courageous commitment to the development of UDC as a strong institution of higher learning has earned him widespread respect.

Dr. Alexander was born in Georgia, attended the public schools from kindergarten through the 12th grade in Cincinnati, and earned his B.A. degree in chemistry at the University of Cincinnati. His Master's degree in chemistry was earned at Bradley University and his doctorate in chemistry at Georgetown University in 1957.

He has received many honors and awards and throughout a busy career has maintained an active interest as a participant in a range of civic movements including the PTA, Boy Scouts, the YMCA, and civic rights activities.

The subject of Dr. Alexander's address is Black Education--its title, "To Find the Solution, Understand the Problem."

It is my honor to present Dr. Ben Alexander -- Dr. Alexander.

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*Director, National Institutes of Health, Bethesda, Maryland.

**February 16, 1983, Masur Auditorium,
Warren G. Magnuson Clinical Center.

REMARKS*

By

James B. Wyngaarden, M.D.**

An assembly of the NIADDK Coalition is an appropriate occasion for a discussion of the National Institutes of Health and the conduct and support of biomedical research in the United States. Your Coalition, while focused on the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, is representative of the Nation's approach to the conquest of disease and disability. Our vast and highly successful research enterprise has thrived in response to challenges and opportunities. Its hallmarks are vigorous competition among scientists and public advocates who, nevertheless, remain united in a common effort to achieve better health for all. We need the spirit of coalition you represent as we work to solve the problems that confront the biomedical research community today. I congratulate you on the formation of the NIADDK Coalition and welcome this opportunity to discuss common concerns with you.

The Institute you support, and the wide range of basic and clinical science investigations it conducts, are representative of the state of biomedical research today. Here, too, one finds diversity and unity as research attacks many disorders while tending increasingly to focus on the cellular and molecular origins of disease, on the discovery of unifying concepts of the processes of life. Discoveries in one field of basic biological science may lead to advances in the treatment or prevention of disease in some quite unforeseen disease category. Cross-fertilization of ideas and collaboration among scientific disciplines are characteristic of the internal work of NIADDK and of its joint ventures with other Institutes and research institutions. NIADDK has been strengthened by its designation last year as a Bureau of the Public Health Service. And Dr. Salans has continued to provide strong and vigorous leadership in his role as the bona fide Director of NIADDK. I look for greater progress than ever in the years ahead as NIADDK pursues the scientific opportunities available today.

Those opportunities grow out of what was termed a "profound development in medical science" by Dr. Arthur Kornberg, Nobel Laureate and member of the NIH Director's Advisory Committee. In a talk last year, Dr. Kornberg described a "confluence of the many discrete and previously unrelated medical science subjects into a single, unified discipline. Anatomy, physiology, biochemistry, microbiology, immunology, and genetics have now merged and are

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*Luncheon Address, Second Annual Meeting of the NIADDK Coalition, February 22, 1983, Marriott Hotel, Bethesda, Maryland.

**Director, National Institutes of Health, Bethesda, Maryland.

expressed in a common language of chemistry," he said, stressing the importance of fundamental research. (1) I am confident that NIADDK will capitalize on the opportunities offered by this development in biomedical science.

This evolution of science has been made possible by a multi-billion-dollar public investment in the past 30 years. Here, again, there is unity in objective and diversity in effort. While the public is the major investor, the Federal Government does not have a monopoly on health science research, as a few statistics will illustrate. The Federal Government supports an estimated 90 percent of basic biomedical research in this country, and more than 60 percent of research and development at American universities and medical schools is funded by NIH. Extramural awards in fiscal year 1982 accounted for 81 percent of the NIH budget of $3.6 billion (SLIDE 1), and 52 percent of awards went to medical schools (SLIDE 2). In other words, the lion's share of biomedical research is conducted in institutions throughout the country, by a coalition of scientific investigators.

Each step in the growth of that research enterprise has been in response to a unique set of circumstances created by the evolution of science, technological development, the changing expectations and priorities of the public as expressed by the Administration, Congress, and groups such as yours, and by economic conditions. Most recently, it has been a combination of economic conditions and changing public perception that has had the greatest influence on our activities. I understand that Dr. Salans brought you up to date this morning on programs, policies, and budgetary matters related directly to NIADDK. I would like to review these topics from an NIH-wide perspective.

A look at how our budget has changed during the last 25 years is instructive. The main NIH program growth came during the decade 1955-1965, with appropriations growing roughly 14-fold. This slide (SLIDE 3) shows the NIH budget in both current and constant dollars from 1972 to 1982. In that decade there was a 15 percent increase in constant dollars, but the growth of indirect costs during this period has almost exactly matched this increment (SLIDE 4) so that the funds available to support the direct costs of research are essentially the same in 1983 as in 1972.

Our peak year was actually in 1979. The budget fell by 12 percent in purchasing power betweeen 1979 and 1982 and rose by 4 percent in 1983 for a net decrease of 8 percent. The fiscal year 1984 budget for NIH submitted to Congress by the President requests $4.077 billion. That represents a $73 million, or 1.8 percent, increase over fiscal year 1983, for which an inflationary rate of 5 percent is predicted.

In short, the NIH budget has been essentially in a steady state for more than a decade, and we cannot expect dramatic increases in the near future, certainly not until the national economy improves. At the same time, biomedical research has received strong support from present and previous Administrations and Congresses, and NIH has fared better than many other agencies in recent years. The importance of the national investment in biomedical research to public health is widely recognized.

Historically we have been accommodating to a relatively constant budget and an increasing number of excellent research proposals by shifting funds among mechanisms. These changes began in 1975 (SLIDE 5) but were not articulated as a policy until fiscal year 1980 when we asked the Congress for sufficient funds to support a minimum of 5,000 new and competing research grants and 10,000 trainees.

With that context in mind, I would like to consider some program and policy issues that face NIH and the research community. Steady-state resources inevitably intensify competition for support in all areas for which NIH is responsible. In addition to extramural research project grants, these include: centers, contracts, clinical trials, research instruments, and facilities, as well as the intramural programs and facilities at NIH. Since our fundamental mission is biomedical research to improve health and well-being, we must also emphasize prevention of disease and disability and make a special effort to see that scientific discoveries are transferred to medical practice as quickly as appropriate.

In awareness of those multiple responsibilities and of fiscal constraints, we have placed the highest priority on these objectives:

- To sustain maximum stability in the investigator-initiated research project base.
- To support the training of an optimum number of new investigators to assure continuity of high-quality research in the future.
- To organize the agency for maximum efficiency in support of modern biomedical research.

We continue to emphasize stability in the research project base because pursuit of fundamental knowledge is the foundation of progress in the health sciences, and investigator-initiated research holds the greatest promise of significant discovery. Our objective is to provide a steady and predictable level of research project support, one that offers continuity to established investigators and their work, and that encourages new scientists to enter the field.

The stabilization policy has in fact done just that. We have been able to dampen large fluctuations in support of new and competing renewal awards. In 1981, we supported 5,109 grants and, in 1982, 5,027 grants.

The 1983 budget will enable us to support some 4,914 new and competing renewal grant awards out of a research grant portfolio of about 16,357. We are also supporting some 9,969 trainees. To achieve that level, however, we have had to shift funds from some mechanisms, most notably clinical trials and initiatives to emphasize special areas or activities, such as research centers. The fiscal year 1984 budget is still being negotiated with OMB. Without additional budgetary shifts, the President's budget would support 3,676 competing awards and 9,105 trainees.

The difficulty of setting priorities among competing demands can be illustrated by examining the changing level of support in various mechanism categories over the past decade.

Given finite resources and a commitment to stability in one growing element among several necessary activities, the ultimate result is destabilization of the others. In fact (SLIDE 6), if the current rate of increase in percent of NIH extramural budget devoted to the research grant component were to continue, it would reach 100 percent around 1993.

Those pressures will intensify in the future because of some trends over which we have little or no control. For example, the average cost per grant has grown faster than the rate of inflation, and indirect costs have increased faster than direct costs. The clearest reflection of this differential occurred in fiscal year 1982. Of $76 million increase for these grants over the previous year, $35 million, or 46 percent, went to indirect costs.

The dilemma is: How are we to ensure that all essential and vital activities are continued while stability in the research and training base is maintained? Many Institute Directors feel that further shifts would seriously limit their ability to meet other program goals and to maintain program balance. This year we are involving the Director's Advisory Committee in a review of the impact of our stabilization policy on all of NIH and particularly on the extramural program. We will also analyze the factors contributing to the increasing cost of research projects, including an analysis of indirect costs and of faculty salary support, with a view toward achieving greater efficiency in the support of research. But I anticipate that, even after careful review, the concept of stabilization will be reaffirmed as a policy.

We are also seeking stability in training of sufficient numbers of investigators to maintain the vitality of research. There are considerations beyond numbers. For example, although there currently is an adequate supply of scientists in most fields, a diminishing proportion of physicians is engaging in NIH-supported research (SLIDE 7). The success rate among applicants for grants is greatest for investigators with combined M.D./Ph.D. degrees, followed by Ph.D.s, with M.D.s last (SLIDE 8).

There are also fewer physicians interested in training themselves as researchers. Of the 2,800 positions that the National Academy of Sciences recommmends be devoted to clinical training, approximately 900 are now filled by Ph.D.s, compared with only 450 several years ago. The major barriers to attracting M.D.s appear to be the perception of instability in support for research; the increasing complexity of science which, in turn, leads to a need for longer training; the widening gap between laboratory and bedside; the debt load incurred by physicians, and the stipend which averages some $6,000 less than an equivalent residency staff position in a hospital. The solutions are also complex, including earlier exposure of students to research experiences; greater flexibility in medical curricula, graduate training and board requirements; a realization among researchers and trainees that a substantial period of training is required; higher stipends for post-M.D. trainees; and an

assurance by Federal agencies of both stability and access to the system by young investigators.

An increase in the physician's stipend might attract M.D.s into research training but, given a limited budget, this would force a reduction in number of trainees. We need to maintain the support level for nonclinical training while finding incentives to encourage more physicians to enter research.

To this end we are considering a new type of training program, perhaps called a Physician-Investigator Development Award Program, which would provide support for five years of full-time research training, including graduate school courses, with a stipend above the residency level. These training programs would be based in departments with established records in producing physician-scientists. This program would not replace current training or fellowship programs and would be smaller in scale, perhaps leveling off at about 400 trainees in three years. The goal would be to raise the total number of M.D. trainees from the present level of 1,900 to about 2,300 per year. NIADDK may be the first Institute to announce such a program.

There are three longer-range issues of interest to the Coalition. Foremost is the need to assure adequate levels of support for the research enterprise. Currently our award rate is 33 percent of approved applications. We believe an optimal level for progress would be 45 to 50 percent. In the context of the Federal budget, the sums needed are not large. To achieve this goal we would need an additional $300-400 million per year for three years, and thereafter an annual budget of $5 billion, adjusted for inflation.

A similar problem exists in replacing or purchasing the increasingly sophisticated research instrumentation our laboratories now require. NIH has estimated that $20 million a year for five years is needed for the acquisition of large-scale shared-instrumentation resources with additional funds for the purchase, via research grants, of smaller instruments.

Finally, extramural laboratories and facilities are slowly deteriorating. With the exception of funds supplied by the Cancer program and, more recently, the Eye Institute, NIH stopped supporting facilities after 1969. We need to help modernize and to construct new laboratories.

I want to emphasize that it is not possible to accomplish these goals in the immediate future. Given the current state of the economy, I believe NIH has fared well. Our budget represents a strong commitment by the Administration to biomedical research. But I also believe that as the economy improves it is imperative to increase that level of support.

There is a continuing issue that raises scientific, budgetary, and administrative problems, one with which the Coalition is familiar, namely, repeated proposals to establish new institutes at NIH. You are all aware, I am sure, that legislation was introduced in the House last week to establish a National Institute of Arthritis and Musculoskeletal Diseases. I must tell you frankly that we--NIH and the Department--will testify in opposition to that proposal. Our position is based on considerations that extend beyond the

immediate proposal. Primarily, our position arises from concern over the ability of NIH to accommodate to changing demands of biomedical science and to provide the most effective management. Given growing public awareness of the potential for successful intervention in disease processes, we can expect continued pressure for additional, narrowly focused research efforts. In recent years, for example, there have been ten proposals for new institutes and five proposals to transfer to NIH functions from other Public Health Service Agencies. In my opinion, additional categorical, disease-specific institutes at NIH would not contribute to most efficient administration of research and would lead to increased administrative costs at the expense of funding for research.

To help resolve questions of NIH organization, we have asked the Institute of Medicine to make an 18-month study of the present structure of the Agency, to examine its adequacy and efficiency, and to devise criteria by which we can evaluate and determine need for future change. I urge you, as representatives of separate organizations and as a Coalition, to participate actively in that study in the months ahead. You will be contributing to an effort that will, in the long run, enable us to make decisions that will strengthen the way in which we conduct and support biomedical research.

In conclusion, I would like to repeat another comment by Arthur Kornberg concerning the need to promote greater public understanding of the importance of basic research. "It was scientific curiosity," Kornberg said, "rather than crusades against disease that gave us X-rays, penicillin and genetic engineering. Sustained and effective propaganda for basic research is terribly important, but this must be the collective responsibility of societies of scientists and informed lay people." (2) He was not speaking specifically of the NIADDK Coalition, but he surely had in mind the vital service you contribute to the advancement of biomedical research and, ultimately, to the conquest of the chronic diseases and disorders that continue to plague us all.

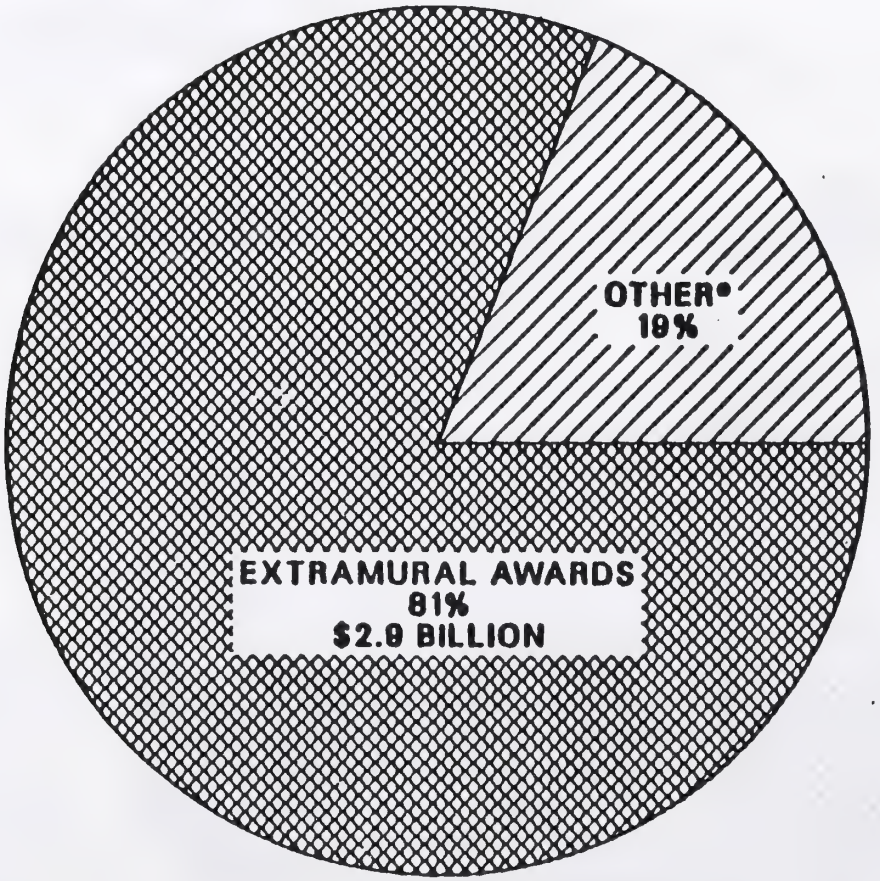
* * * * *

REFERENCES

1. Kornberg, Arthur. "Biology and Technology," Address, San Francisco, California, April 13, 1982, p. 6.

2. Ibid., "Confluence of the Medical Sciences," Address, Pittsburgh, Pennsylvania, February, 1981, p. 9.

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET
FISCAL YEAR 1982

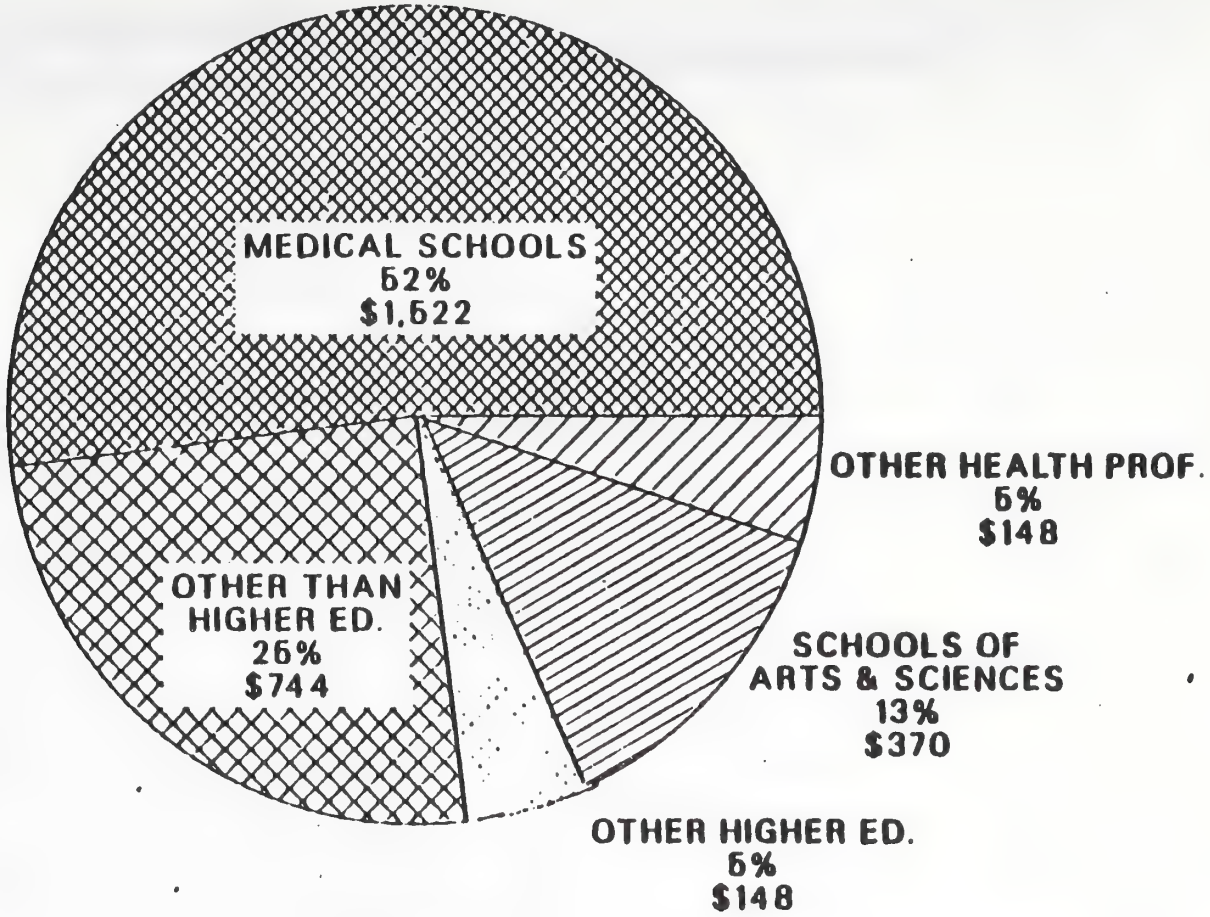


TOTAL - $3.6 BILLION

*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



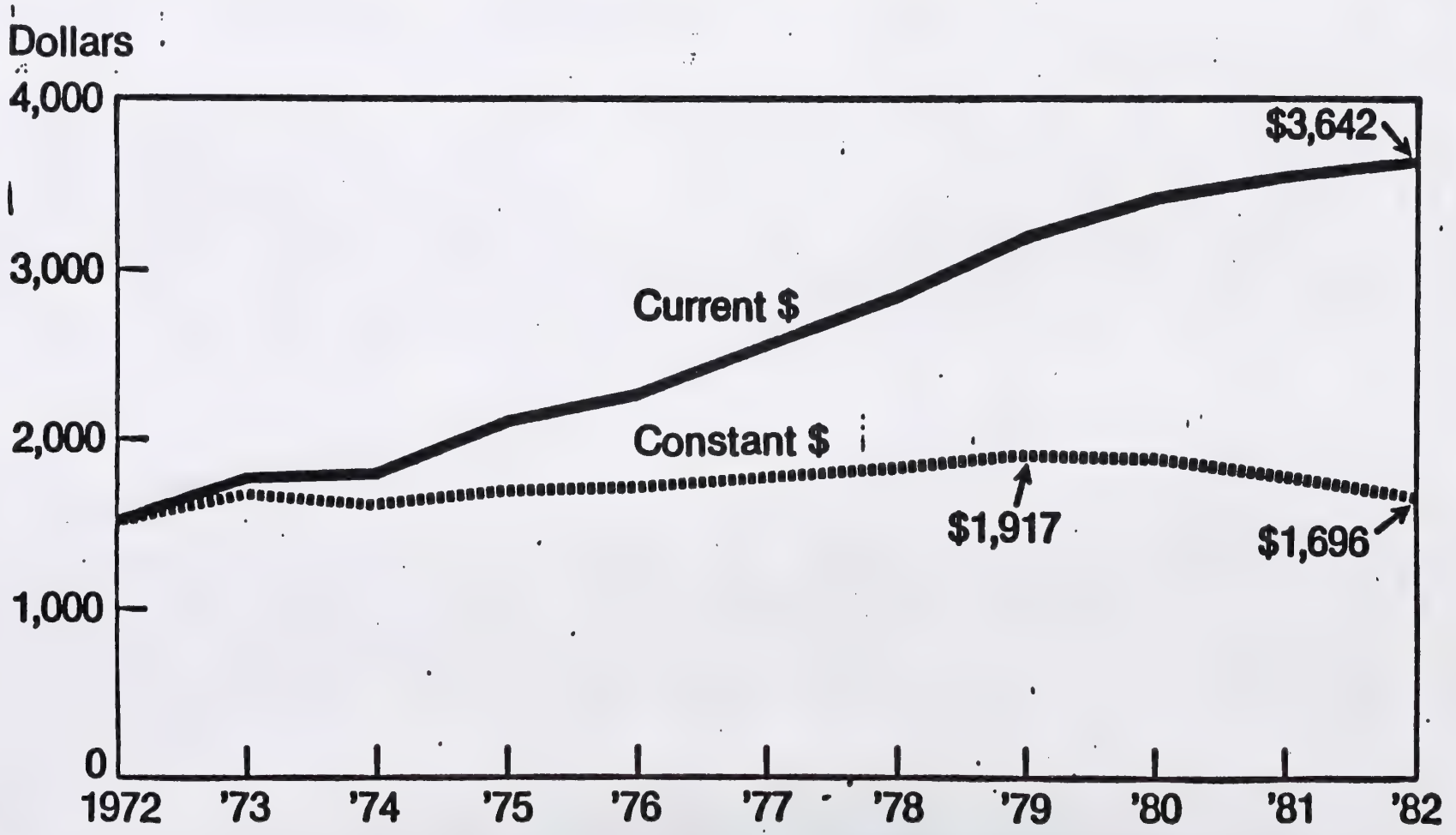
FY 1982*

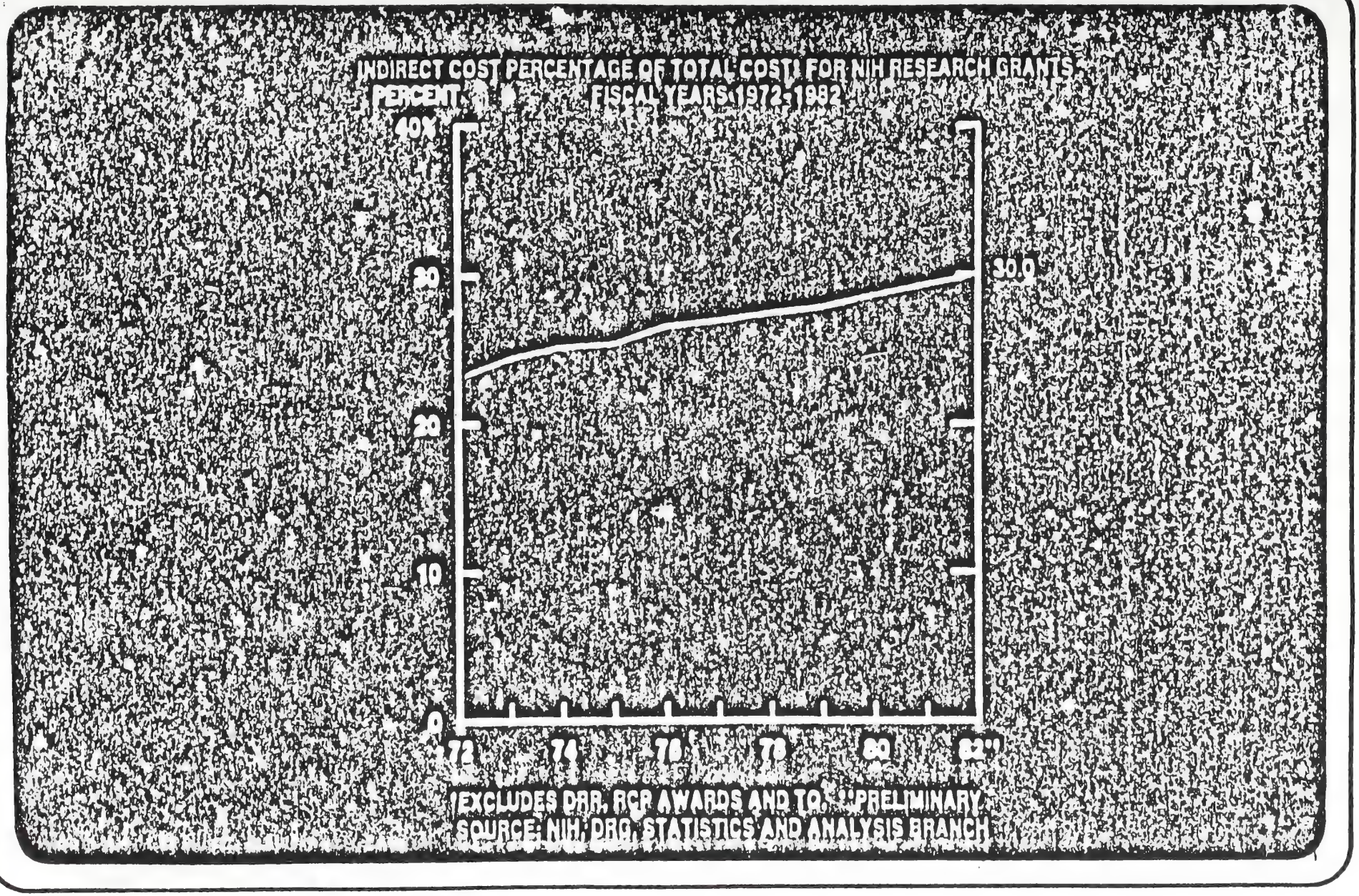
$2,933 MILLION

*PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Total NIH Appropriations, 1972-82

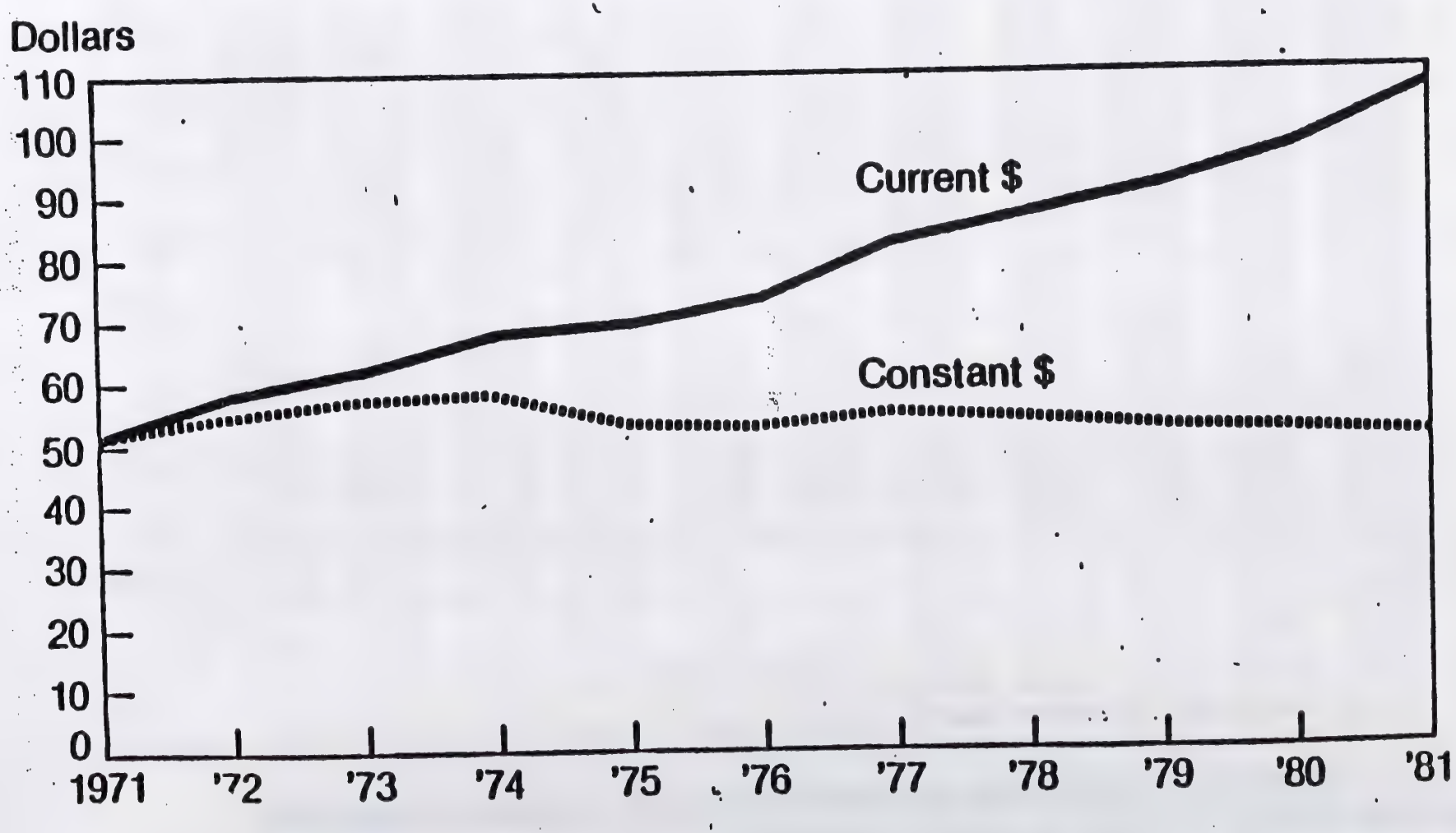
In Current and Constant Dollars (Millions)



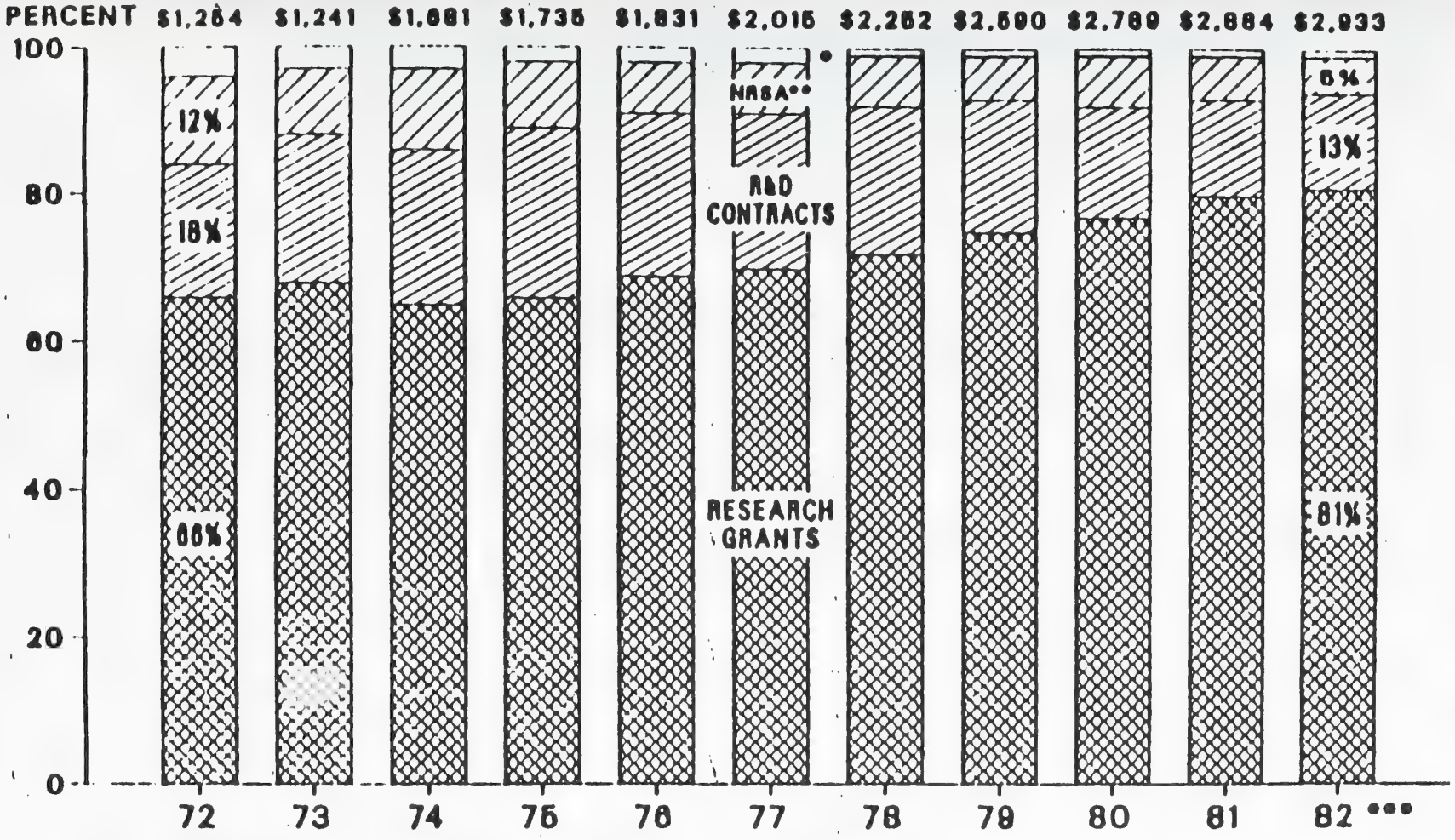

INDIRECT COST PERCENTAGE OF TOTAL COSTS FOR NIH RESEARCH GRANTS
PERCENT
FISCAL YEARS 1972-1982
40%
30
20
10
0
30.0
72
74
76
78
80
82 (P)
(EXCLUDES DRR, RCR AWARDS AND TO
PRELIMINARY
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Average Research Project Grant, 1971-81

In Current and Constant Dollars (Thousands)

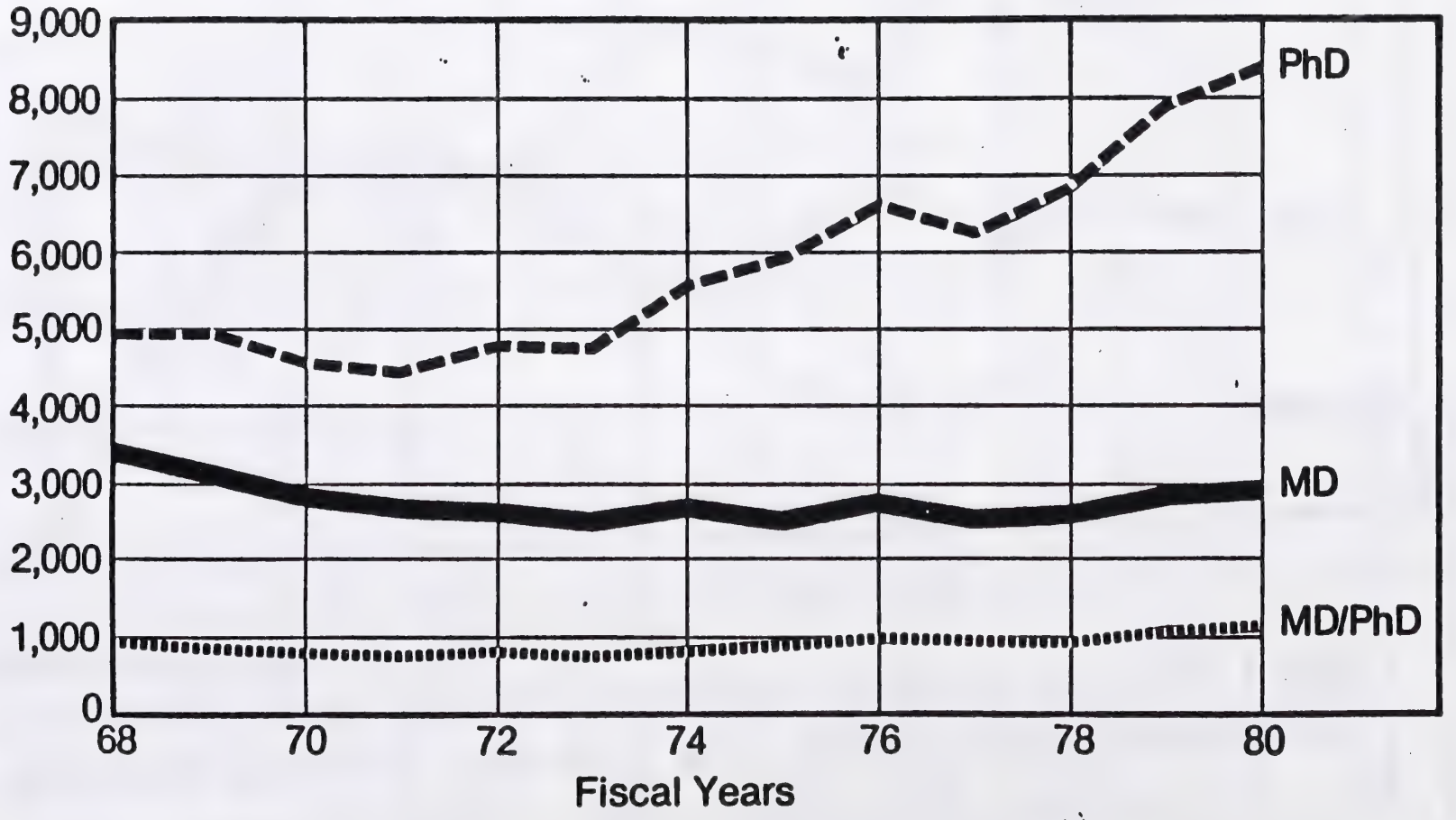


ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)

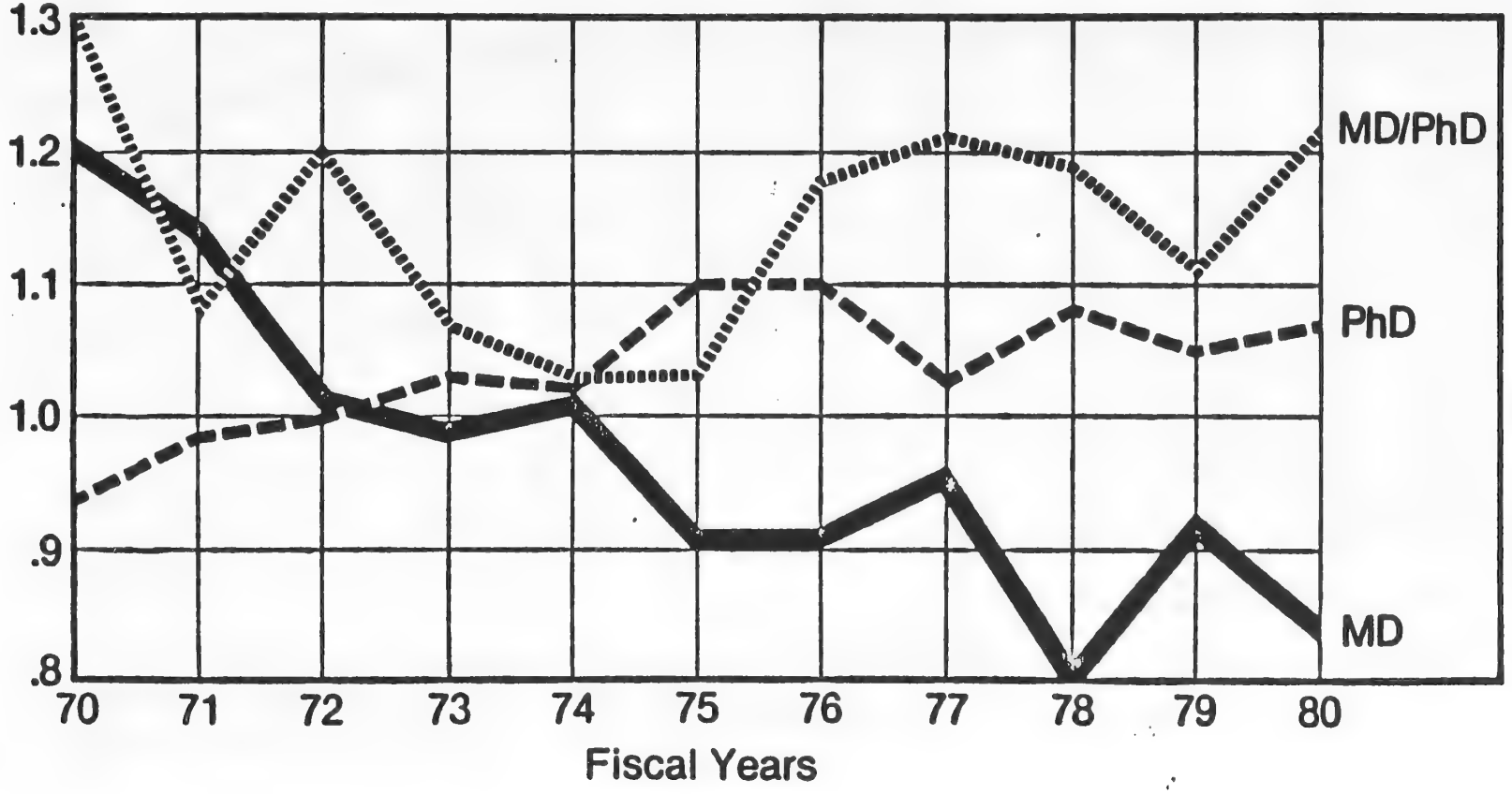


NOTE: EXCLUDES TQ. *INCLUDES CONSTRUCTION, CONTROL, AND MEDICAL LIBRARY GRANTS.
**INCLUDES PRE-NRSA TRAINING. ***PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

Number of P.I.'s on All R01 Grants Holding MD, PhD or MD/PhD Degrees



Success Rates of New MD, PhD and MD/PhD Applicants Compared with Average Success Rates of All Type 1 R01 Applicants in the Same Year



"THE FEDERAL-ACADEMIC PARTNERSHIP IN BIOMEDICAL RESEARCH"*

by

JAMES B. WYNGAARDEN, M.D.**

AS WE BEGIN, I WOULD LIKE TO EXPRESS MY APPRECIATION TO DUKE UNIVERSITY FOR THE INVITATION TO PARTICIPATE IN THE ROUNDTABLE ON SCIENCE AND PUBLIC AFFAIRS. THE INVITATION CAME ORIGINALLY FROM BILL BEVAN. I UNDERSTAND THAT WHEN HE DISCOVERED THAT THE ADDRESS WAS SCHEDULED FOR THE SAME EVENING AS THE DUKE-NC STATE BASKETBALL GAME, HE PROMPTLY TOOK A JOB WITH THE McARTHUR FOUNDATION. I HAVE HESITATED TO SAY ANYTHING TO BILL ABOUT THE CONFLICT, SINCE HE NOW HEADS A GROUP THAT MAKES LIFETIME GRANTS TO INDIVIDUALS TO SIT AND THINK. AND SINCE I HAVE LITTLE TIME TO DO EITHER IN MY PRESENT JOB, AND SERVE AT THE PLEASURE OF THE PRESIDENT, I DON'T WANT TO OFFEND BILL. I JUST DON'T KNOW HOW SOON I MAY BE CALLING HIM ABOUT ONE OF THOSE AWARDS.

WHEN BILL FIRST CALLED ABOUT THIS EVENING'S EVENT, I WAS FLATTERED AND PLEASED TO BE INVITED BACK TO DUKE AND QUICKLY ACCEPTED. I HAVE ENJOYED THIS SERIES OVER THE YEARS AND WAS HONORED TO BE INVITED TO PARTICIPATE.

A FEW WEEKS LATER THERE CAME AN URGENT REQUEST FOR A TITLE. I DID WHAT MOST SPEAKERS DO WHEN HARASSED BY SENSORY OVERLOAD AND WHEN REQUIRED TO THINK MOMENTARILY ABOUT AN EVENT FAR IN THE FUTURE: THEY CHOOSE A SOMEWHAT GRAND AND UTTERLY NONDESCRIPT TITLE THAT WILL PERMIT THEM TO SAY WHATEVER IS ON THEIR MINDS WHEN THAT FUTURE DATE ARRIVES. I NOW RECOIL A BIT AT THE SWEEP AND AMBITION, PERHAPS EVEN THE PRESUMPTION, OF THE TITLE. A MORE APPROPRIATE DESCRIPTION WOULD BE "SOME PERSONAL AND FALLIBLE THOUGHTS ON THE FEDERAL-ACADEMIC PARTNERSHIP IN BIOMEDICAL RESEARCH."

I WAS, OF COURSE, AWARE THAT THIS INVITATION CAME TO ME AS THE RELATIVELY NEW DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH. I HAVE NOW BEEN IN MY POSITION ABOUT TEN MONTHS. IT HAS BEEN A TIME OF EXTRAORDINARY LEARNING FOR ME. ONE OF THE FIRST THINGS I LEARNED WAS THAT I HAD TO BE CAREFUL IN SUGGESTING THAT SOMETHING BE DONE, BECAUSE THERE WAS A HIGH PROBABILITY THAT SOMEONE WOULD DO IT. I NEVER HAD THAT PROBLEM AT DUKE. ONE OF THE EARLY SURPRISES WAS THE INTENSITY OF THE INTERACTIONS BETWEEN NIH AND A MULTITUDE OF SPECIAL INTEREST GROUPS AND THEIR WASHINGTON REPRESENTATIVES, AS WELL AS WITH THE MEMBERS OF

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*Roundtable on Science and Public Affairs, Duke University, Durham, North Carolina, February 23, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

CONGRESS. I WAS ASTONISHED TO LEARN THAT CONGRESSMEN MAKE DEALS IN ORDER TO GAIN SUPPORT FOR THEIR PET PROJECTS, AND ALSO THAT THE ADMINISTRATION SOMETIMES ABRUPTLY CHANGES ITS MIND UNDER INTERESTING CIRCUMSTANCES. I WASN'T AWARE OF THAT BEFORE. I NOW UNDERSTAND WHAT IS MEANT BY THE SAYING THAT THERE ARE TWO THINGS YOU DO NOT WANT TO KNOW HOW THEY ARE MADE. ONE IS SAUSAGE AND THE OTHER IS LEGISLATION.

AS A CONSEQUENCE OF SOME OF MY EXPERIENCES, I HAVE BECOME A MARXIST—A GROUCHO MARXIST. GROUCHO OBSERVED "EVERYONE IN GOVERNMENT IS CONSTANTLY LOOKING FOR PROBLEMS, FINDING THEM EVERYWHERE, MAKING THE WRONG DIAGNOSES, AND PROPOSING THE WRONG SOLUTIONS." IN CONSEQUENCE, MUCH OF WHAT I DO COULD BE CALLED "DAMAGE CONTROL." I RECENTLY VISITED INDIA IN CONNECTION WITH OUR BILATERAL AGREEMENT IN BIOMEDICAL RESEARCH. WE ARE ABOUT TO SEND THEM SOME ARMADILLOS FOR LEPROSY RESEARCH. IT OCCURRED TO ME THAT AN ARMADILLO SHELL COULD BE VERY USEFUL IN WASHINGTON!

BUT IRRESPECTIVE OF THE PROCESS, MANY OF THE LAWS PASSED BY CONGRESS ARE WISE, VISIONARY, AND OF ENORMOUS BENEFIT TO AMERICA's PEOPLE AND INSTITUTIONS. I PLACE THE SUCCESSION OF LAWS THAT ESTABLISHED AND MOLDED NIH IN THAT CATEGORY. THE NIH-UNIVERSITY PARTNERSHIP IS A UNIQUE AMERICAN SUCCESS STORY, ONE THAT HAS BEEN EXTRAORDINARILY PRODUCTIVE IN RESEARCH DISCOVERY AND ADVANCEMENT OF HEALTH, ONE THAT HAS BROUGHT THE UNITED STATES INTERNATIONAL PRESTIGE.

THE ACCOMPLISHMENTS OF THIS JOINT ENDEAVOR HAVE BENEFICIALLY TOUCHED THE LIVES OF MOST PEOPLE DIRECTLY OR INDIRECTLY AND PROMISE EVEN MORE FOR THE FUTURE. SO I ADDRESS THE SUBJECT IN THE CONFIDENCE THAT THE PARTNERSHIP IS A MATTER OF NATIONAL CONSEQUENCE. THUS I CAN TALK ABOUT THE SUBJECT WITH THE ENTHUSIASM THAT COMES FROM KNOWING THAT THE JOINT ENDEAVOR IS SUCCESSFUL.

I DON'T PRETEND THAT I CAN TAKE A DETACHED VIEW OF THE PARTNERSHIP FOR I HAVE WORKED WITH ONE OR THE OTHER OF THE PARTNERS FOR ALL OF MY PROFESSIONAL CAREER. MOST OF THE TIME I WAS ON THE ACADEMIC SIDE, BUT ONE ACCUMULATES EXPERIENCE RATHER RAPIDLY IN THE EXTRATERRESTRIAL WORLD OF WASHINGTON, AND WITH IT A DIFFERENT POINT OF VIEW. I LIKE TO THINK IT IS VISTAVISION RATHER THAN GUN-BARREL VISION IN ANOTHER DIRECTION.

EVEN A CURSORY EXAMINATION OF THE FACTS AND FIGURES DESCRIPTIVE OF THE PARTNERSHIP GIVES AN IMPRESSIVE PICTURE OF ITS MAGNITUDE AND SIGNIFICANCE TO AMERICAN SCIENCE.

THE FEDERAL GOVERNMENT SUPPORTS AN ESTIMATED 90 PERCENT OF BASIC BIOMEDICAL RESEARCH IN THIS COUNTRY. MORE THAN 60 PERCENT OF RESEARCH AND DEVELOPMENT AT AMERICAN UNIVERSITIES AND MEDICAL SCHOOLS IS FUNDED BY ONE FEDERAL AGENCY, THE NATIONAL INSTITUTES OF HEALTH.

MOST OF MY COMMENTS ABOUT THE FEDERAL ACADEMIC RELATIONSHIP WILL REFER TO THE NIH-ACADEMIC PARTNERSHIP, FIRST BECAUSE IT REPRESENTS THE MAJOR PORTION OF THE JOINT ENDEAVOR AND ALSO BECAUSE I CAN SPEAK OF IT FROM FIRST-HAND KNOWLEDGE.

(SLIDE 1)

IN THE CURRENT FISCAL YEAR, NIH EXPENDITURES IN GRANTS AND CONTRACTS FOR RESEARCH AND TRAINING WILL AMOUNT TO WELL OVER THREE BILLION DOLLARS REPRESENTING ABOUT 78 PERCENT OF OUR TOTAL BUDGET.

ABOUT HALF OF OUR AWARDS WILL GO TO MEDICAL SCHOOLS--A PROPORTION THAT HAS RUN BETWEEN 49 AND 52 PERCENT SINCE 1975.

(SLIDE 2)

MORE THAN 1200 INSTITUTIONS, INCLUDING ALL OF THE COUNTRY'S MAJOR UNIVERSITIES, 122 MEDICAL SCHOOLS AND MANY TEACHING HOSPITALS CARRY OUT RESEARCH AND TRAINING SUPPORTED BY NIH.

THE LATEST COUNT OF THE NUMBER OF SALARIED POSITIONS SUPPORTED BY NIH GRANTS WAS MADE IN 1978. AT THAT TIME, A TOTAL OF 102,953 POSITIONS WERE FUNDED THROUGH OUR EXTRAMURAL GRANTS. OF THESE RESEARCH POSITIONS, 47,980 WERE OCCUPIED BY PROFESSIONAL LEVEL SCIENTISTS—THE LARGEST PORTION BEING ACADEMIC FACULTY MEMBERS. BUT, OF COURSE, THE STRENGTH OF OUR PARTNERSHIP IN RESEARCH IS DETERMINED BY THE QUALITY RATHER THAN THE QUANTITY OF THE SCIENTISTS INVOLVED. BY ANY CRITERION, THE PROGRAMS OF THE NIH ENLIST THE CREAM OF AMERICAN SCIENTISTS.

FOR EXAMPLE, OF THE 38 AMERICANS NAMED AS NOBEL LAUREATES IN PHYSIOLOGY OR MEDICINE OVER THE PAST 25 YEARS, 33 (OR 86 PERCENT) EITHER HAD WORKED AT THE NIH OR HAD BEEN SUPPORTED IN THEIR ACADEMIC SETTING BY THE NIH <u>BEFORE</u> BEING AWARDED THE PRIZE.

IN ADDITION, ELEVEN OF THE FOURTEEN AMERICAN LAUREATES IN CHEMISTRY OF THE PAST QUARTER CENTURY HAD A PRIOR CONNECTION WITH THE NIH.

ANOTHER DIMENSION OF OUR JOINT ENDEAVOR RELATES TO THE TRAINING OF FUTURE SCIENTISTS. ALMOST 10,000 POST-DOCTORAL TRAINEES AT ACADEMIC INSTITUTIONS THROUGHOUT THE COUNTRY ARE BEING SUPPORTED THROUGH NIH TRAINING PROGRAMS.

FINALLY, I WANT TO CITE ANOTHER FACET OF THE RELATIONSHIP--THE ROLE OF THOUSANDS OF AMERICAN SCIENTISTS AS RESPONSIBLE ADVISORS AT PRACTICALLY EVERY LEVEL OF NIH RESEARCH ACTIVITIES, PARTICULARLY THE PART THEY PLAY IN REVIEWING RESEARCH PROPOSALS.

AT LEAST THREE TIMES EACH YEAR, SOME 2000 SENIOR SCIENTISTS COME TO BETHESDA AS MEMBERS OF THE 104 INITIAL REVIEW GROUPS TO EXAMINE, DISCUSS AND EVALUATE THE MORE THAN TWENTY THOUSAND GRANT PROPOSALS WE RECEIVE ANNUALLY.

THE CONSIDERED OPINIONS OF OUR ADVISORS ARE CRITICALLY IMPORTANT IN SELECTING THE PROJECTS TO BE FUNDED, BECAUSE IN RECENT YEARS WE HAVE BEEN ABLE TO SUPPORT ONLY ABOUT ONE-THIRD OF THE ELIGIBLE PROJECTS.

MORE THAN EVER BEFORE, THE SEARCH FOR NEW BIOMEDICAL KNOWLEDGE IS INFLUENCED BY THE EXPERT JUDGMENTS OF OUR ADVISORS AS THEY RECOMMEND PRIORITIES FOR INDIVIDUAL PROPOSALS. WE ARE FORTUNATE TO HAVE ACCESS TO THIS TREMENDOUSLY VALUABLE RESOURCE. EQUALLY VALUABLE ADVISORY BODIES ASSIST US IN MANY OTHER ASPECTS OF NIH PROGRAMS INCLUDING THE SUBSTANTIAL RESEARCH ACTIVITIES CONDUCTED IN-HOUSE.

SOMETIMES THIS BUSINESS OF SETTING PRIORITIES IN THE FULL KNOWLEDGE THAT ONLY THE BEST RESEARCH CAN BE FUNDED IS AN UNCOMFORTABLE EXPERIENCE FOR THE PARTICIPANTS, A LITTLE LIKE PLAYING GOD. IT REMINDS ME OF A STORY ABOUT CHILDREN WHO WERE ASKED TO DRAW IN CLASS. MOST DREW A HOUSE, OR A TREE, OR A DOG. ONE GIRL DREW AN ABSTRACTION. THE TEACHER ASKED HER WHAT SHE WAS DRAWING. "I'M DRAWING GOD," SHE SAID. "NO ONE KNOWS WHAT GOD LOOKS LIKE," SAID THE TEACHER, TO WHICH THE YOUNG ARTIST REPLIED, "THEY WILL WHEN I FINISH."

AT THE HEART OF AN OBJECTIVE APPRAISAL OF THE FEDERAL-ACADEMIC PARTNERSHIP, HOWEVER, IS CONSIDERATION OF ITS EFFECT AS AN INSTRUMENT FOR INCREASING KNOWLEDGE FOR THE IMPROVEMENT OF HEALTH AND THE PREVENTION OF DISEASE. HAS IT WORKED?

I WILL STATE THE OBVIOUS--BIOMEDICAL SCIENCE IN THIS COUNTRY AND ELSEWHERE HAS EXPERIENCED A VERITABLE EXPLOSION OF NEW KNOWLEDGE THAT PROMISES A FURTHER CASCADE OF NEW DISCOVERIES. FOR EXAMPLE, LAST SUNDAY's NEW YORK TIMES CALLED THE DISCOVERY OF ONCOGENES THE SINGLE MOST IMPORTANT OBSERVATION IN ALL OF CANCER RESEARCH OVER MANY DECADES AND THE POTENTIAL OF MONOCLONAL ANTIBODIES TO SEEK OUT AND DESTROY MALIGNANT CELLS A MOST SIGNIFICANT DIAGNOSTIC ADVANCE.

THE FEDERAL-ACADEMIC PARTNERSHIP HAS BEEN A MAJOR FORCE IN THE SPECTACULAR EXPANSION OF THE FRONTIERS OF KNOWLEDGE.

PERMIT ME ONE MORE OBSERVATION ABOUT THE NATURE OF THE NIH-ACADEMIC PARTNERSHIP, PARTICULARLY THE MECHANISM I CONSIDER TO BE THE PRINCIPAL SOURCE OF ITS EFFECTIVENESS. ALMOST EXACTLY HALF OF THE AGENCY's BUDGET THIS YEAR, AS IN THE SEVERAL PREVIOUS YEARS, IS ASSIGNED TO THE SUPPORT OF INVESTIGATOR-INITIATED RESEARCH PROJECT GRANTS. THIS MEANS THAT OUR JOINT RESEARCH EFFORT IS BUILT ON THE BROADEST POSSIBLE BASE--THAT THE RANGE OF ABILITIES REPRESENTED BY THE SCIENTISTS WHOSE IDEAS ARE OFFERED FOR SUPPORT EXTENDS FAR BEYOND THE CREATIVE SCOPE THAT COULD BE FOUND IN ANY SINGLE AGENCY OR INSTITUTION, NO MATTER HOW LARGE, OR ANY CONSORTIUM OF SUCH ESTABLISHMENTS. THE GRANT MECHANISM NOT ONLY ATTRACTS CREATIVE IDEAS FROM ACROSS THE ENTIRE RESEARCH COMMUNITY—IT OFFERS REASONABLE ASSURANCE THAT AT LEAST A SUBSTANTIAL NUMBER OF THE BEST RESEARCH PROPOSALS WILL BE SUPPORTED.

IN ADDITION, THE JOINT VENTURE HAS GREATLY STRENGTHENED THE UNIVERSITY IN SCIENCE TEACHING AND IN COMMUNITY SERVICE. THE AUDITORIUM IN THE CLINICAL CENTER AT THE NATIONAL INSTITUTES OF HEALTH HAS A QUOTATION FROM ITS FIRST DIRECTOR, DR. JACK MASUR, ENGRAVED IN THE MARBLE WALL AT ITS ENTRANCE THAT BEAUTIFULLY CAPTURES THIS CONCEPT: "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING, TEACHING LIFTS THE STANDARDS OF SERVICE, AND SERVICE OPENS NEW AVENUES OF INVESTIGATION." FOR "HOSPITALS" ONE COULD EQUALLY WELL READ "UNIVERSITIES."

IN SKETCHING THE STATUS OF THE PARTNERSHIP, I HAVE PRESENTED A HIGH-KEY OUTLINE WITHOUT REFERENCE TO THE FUTURE OR TO THE CHALLENGES WE MUST FACE TOGETHER.

BEFORE ADDRESSING SOME OF THE ISSUES THAT MUST BE RESOLVED, I BELIEVE IT USEFUL TO NOTE THAT THE FEDERAL RESEARCH PARTNERSHIP WITH ACADEMIC MEDICAL INSTITUTIONS IS A COMPARATIVELY RECENT DEVELOPMENT.

THE NIH WILL OBSERVE ITS CENTENNIAL IN FOUR YEARS, BUT FOR MORE THAN HALF OF ITS HISTORY, THE AGENCY HAD LITTLE OR NO CONTACT WITH ACADEMIC INSTITUTIONS.

WITH THE COMING OF THE "NEW DEAL" IN THE THIRTIES, THE FEDERAL GOVERNMENT ENTERED INTO MANY NEW RELATIONSHIPS WITH PRIVATE AND PUBLIC ORGANIZATIONS, BUT EVEN THOUGH HEALTH RESEARCH WAS CONDUCTED BY THE FEDERAL GOVERNMENT, THIS ACTIVITY DID NOT EXTEND TO SUPPORT OF RESEARCH IN ACADEMIC INSTITUTIONS.

THE PARTNERSHIP WE ARE DISCUSSING HAD ITS REAL BEGINNINGS IN THE WAR EFFORTS OF THE EARLY 1940s. WHILE IN WORLD WAR I THE UNIVERSITIES HAD ONLY BEEN A SOURCE OF RAW RECRUITS, IN WORLD WAR II THE MAJOR UNIVERSITIES WERE ENLISTED IN NATIONAL DEFENSE AND IN SCIENTIFIC AND TECHNICAL DEVELOPMENT AS NEVER BEFORE.

FROM THE PERSPECTIVE OF BIOMEDICAL RESEARCH, THE ACTIVE PARTNERSHIP OF THE FEDERAL GOVERNMENT AND ACADEMIC SCIENCE BEGAN UNDER THE PRESSURES OF WORLD WAR II WHEN IN ORDER TO INITIATE AND SUPPORT SCIENTIFIC RESEARCH ON MEDICAL PROBLEMS AFFECTING THE NATIONAL DEFENSE, THE GOVERNMENT TURNED TO THE ACADEMIC SECTOR.

IN 1941 ONLY SIX OF THE 71 FOUR-YEAR AMERICAN MEDICAL SCHOOLS REPORTED ANY INCOME FROM THE FEDERAL GOVERNMENT. THE GRAND TOTAL OF SUCH SUPPORT WAS LESS THAN $200,000.

BY LATE 1944, THERE WERE ALMOST 500 FEDERALLY SUPPORTED MEDICAL RESEARCH PROJECTS AT 120 DIFFERENT INSTITUTIONS. OVER 95 PERCENT OF THESE RESEARCH PROJECTS WERE CONDUCTED AT UNIVERSITIES, MEDICAL SCHOOLS, OR TEACHING HOSPITALS. DURING THE DEMOBILIZATION PERIOD, THE DECISION WAS MADE TO ASSIGN THE ADMINISTRATION OF ONGOING HEALTH RESEARCH PROJECTS TO THE NATIONAL INSTITUTES OF HEALTH SO THAT WHEN THE FEDERAL OFFICE OF SCIENTIFIC AND RESEARCH DEVELOPMENT WENT OUT OF BUSINESS ON JANUARY 1, 1946, SOME 250 PROJECTS TOTALING $800,000 WERE TAKEN OVER BY NIH'S RESEARCH GRANTS OFFICE.

OUT OF THE WARTIME EXPERIENCE, IT WAS RECOGNIZED THAT FEDERAL SUPPORT OF RESEARCH WAS NOT ONLY APPROPRIATE BUT, MORE IMPORTANTLY, THAT IT COULD BE HIGHLY PRODUCTIVE.

I WILL NOT DWELL ON THE HISTORY OF THE NIH OTHER THAN TO NOTE THAT DURING THE IMMEDIATE POSTWAR PERIOD, THE ORGANIZATION AS IT STANDS TODAY BEGAN TO BE FORMED. CONCURRENTLY, THE PARTNERSHIP WAS STRENGTHENED AND ENLARGED. BY 1948 ALL BUT TWO OF THE 71 AMERICAN FOUR-YEAR MEDICAL SCHOOLS REPORTED RECEIVING FEDERAL GRANTS. THE TOTAL WAS ABOUT $10.5 MILLION IN 1948.

BY THE MID-FIFTIES, THE OVERALL BUDGET OF THE NIH HAD GROWN TO $82 MILLION OF WHICH TWO-THIRDS WAS SPENT FOR GRANTS.

THEN, AS NOW, THE MAJOR INSTRUMENT WAS THE PROJECT GRANT TO SUPPORT THE WORK OF INDIVIDUAL SCIENTISTS. IN THIS EARLY PERIOD OF THE MODERN NIH, THE PEER REVIEW SYSTEM WAS DEVELOPED AS A MEANS FOR ASSESSING THE MERIT OF GRANT PROPOSALS. IN THE SUCCEEDING YEARS, THIS CONCEPT HAS PROVED ITS WORTH AS AN INDISPENSABLE ELEMENT IN THE OPERATION OF NIH PROGRAMS. THE CONGRESS HAS TAKEN

NOTE OF THE PEER REVIEW SYSTEM AND HAS MADE IT A REQUIREMENT FOR GOVERNING OUR PROGRAMS.

BY 1955 THE TIME WAS RIPE FOR MASSIVE EXPANSION OF NIH. DURING THE DECADE THAT FOLLOWED, THE TOTAL NIH BUDGET GREW TWELVEFOLD AND EXPENDITURES FOR GRANTS FIFTEENFOLD. THE OVERALL NIH BUDGET REACHED $1. BILLION FOR THE FIRST TIME IN 1966.

THIS PERIOD OF SPECTACULAR GROWTH INDICATES A FIRM ACCEPTANCE BY THE FEDERAL GOVERNMENT OF AN ESTABLISHED POLICY ON BIOMEDICAL RESEARCH.

FUNDAMENTAL TO THAT POLICY IS THE ASSUMPTION BY THE FEDERAL GOVERNMENT OF A MAJOR SHARE OF THE RESPONSIBILITY FOR SUPPORT OF BIOMEDICAL RESEARCH--BASIC RESEARCH IN PARTICULAR.

A SECOND ELEMENT OF THE POLICY WAS THE CONTINUED HEAVY RELIANCE ON NON-FEDERAL INVESTIGATORS AND INSTITUTIONS AS PARTNERS IN THE FEDERAL RESPONSIBILITY FOR BIOMEDICAL RESEARCH.

WITHIN THE BROAD BOUNDS OF THAT POLICY, THE NIH HAS CONTINUED TO GROW--BUT IT WOULD HAVE BEEN UNREALISTIC TO EXPECT THE RATE OF GROWTH TO MATCH THAT OF EARLIER YEARS.

BUT MANY OF US WERE BADLY SPOILT, PARTICULARLY THE GENERATION OF NOW SENIOR RESEARCH SCIENTISTS PRIVILEGED TO MATURE IN AN ERA MARKED BY REGULAR ANNUAL INCREASES IN THE FUNDS AVAILABLE TO SUPPORT OUR RESEARCH. THERE WERE, TO BE SURE, A FEW JEREMIAHS WHO PROPHESIED THAT AN ANNUAL 15 PERCENT INCREASE IN THE RESEARCH BUDGET AND AN ANNUAL 3-6 PERCENT INCREASE IN THE GROSS NATIONAL PRODUCT COULD NOT PERSEVERE INDEFINITELY. THOSE WHO ENJOYED SUCH MISCHIEF DELIGHTED IN IDENTIFYING THE YEAR WHEN THE ENTIRE FEDERAL BUDGET WOULD BE DIRECTED TOWARD SCIENTIFIC RESEARCH. YET WE BLITHELY WENT AHEAD ASSUMING THAT THE APPROPRIATIONS FOR SCIENTIFIC RESEARCH WOULD ALWAYS TAKE CARE OF OUR NEEDS. THE FAILING IS HUMAN. WE CONTINUE TO BEHAVE AS THOUGH THE WORLD'S PETROLEUM RESERVES AND MINERAL DEPOSITS ARE INEXHAUSTIBLE.

IN 1975 THE APPROPRIATION FOR THE NIH EXCEEDED $3 BILLION FOR THE FIRST TIME. BUT, IN THE PAST DECADE, THE GROWTH IN SUPPORT HAS BEEN MORE APPARENT THAN REAL.

(SLIDE 3)

THE 1979 APPROPRIATION OF $3.2 BILLION REPRESENTS AN ALL-TIME HIGH IN CONSTANT DOLLARS BUT WAS WORTH ONLY $1.92 BILLION IN 1972 DOLLARS, AND BETWEEN

1979 AND 1982, THE FLOW OF CONSTANT DOLLARS FELL BY 12 PERCENT. A SLIGHT INCREASE IN THE 1983 BUDGET, BRINGING THE 1972 CONSTANT DOLLAR LEVEL BACK TO $1.77 BILLION, INDICATES THAT FOR THE PRESENT AT LEAST THE DECLINE IN PURCHASING POWER HAS LEVELED OFF.

THE FISCAL YEAR 1984 BUDGET FOR NIH, SUBMITTED TO THE CONGRESS BY THE PRESIDENT ON JANUARY 31, CALLS FOR $4.077 BILLION. THAT REPRESENTS A $73 MILLION, OR 1.8 PERCENT INCREASE OVER THE CURRENT FISCAL YEAR FOR WHICH AN INFLATIONARY RATE OF FIVE PERCENT IS PREDICTED.

IN SHORT, THE NIH BUDGET HAS BEEN ESSENTIALLY IN A STEADY STATE FOR MORE THAN A DECADE AND WE CANNOT EXPECT DRAMATIC INCREASES IN THE NEAR FUTURE, CERTAINLY NOT UNTIL THE NATIONAL ECONOMY IMPROVES. AT THE SAME TIME, BIOMEDICAL RESEARCH HAS RECEIVED STRONG SUPPORT FROM PRESENT AND PREVIOUS ADMINISTRATIONS AND CONGRESSES AND HAS FARED BETTER THAN MANY OTHER FIELDS, SUCH AS PHYSICS AND ENGINEERING, IN RECENT YEARS.

OVER THE PAST DECADE NIH HAS BEEN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET AND HAS FUNDED AN INCREASING NUMBER OF EXCELLENT RESEARCH PROPOSALS BY SHIFTING FUNDS AMONG OUR VARIOUS PROGRAM MECHANISMS.

(SLIDES 4 and 5)

THESE CHANGES BEGAN IN 1974 BUT WERE NOT ARTICULATED AS A POLICY UNTIL FISCAL YEAR 1980 WHEN WE ASKED THE CONGRESS FOR SUFFICIENT FUNDS TO SUPPORT A MINIMUM OF 5000 NEW AND COMPETING RESEARCH GRANTS AND 10,000 TRAINEES.

WE CONTINUE TO EMPHASIZE STABILITY IN THE RESEARCH PROJECT BASE BECAUSE PURSUIT OF FUNDAMENTAL KNOWLEDGE IS THE FOUNDATION OF PROGRESS IN THE HEALTH SCIENCES AND INVESTIGATOR-INITIATED RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERIES. OUR OBJECTIVE IS TO PROVIDE A STEADY AND PREDICTABLE LEVEL OF RESEARCH PROJECT SUPPORT, ONE THAT OFFERS CONTINUITY TO ESTABLISHED INVESTIGATORS AND THAT ENCOURAGES NEW SCIENTISTS TO ENTER THE FIELD.

THE STABILIZATION POLICY HAS IN FACT DONE JUST THAT. WE HAVE BEEN ABLE TO DAMPEN LARGE FLUCTUATIONS IN SUPPORT OF NEW AND COMPETING RENEWAL AWARDS. IN 1981 WE SUPPORTED 5,109 SUCH GRANTS, AND IN 1982, 5,027. THESE GRANTS WERE IN ADDITION TO THE 11-12,000 CONTINUING GRANTS THAT CARRIED OVER FROM YEAR TO YEAR. OUR AVERAGE GRANT IS AWARDED FOR A PERIOD OF THREE TO FOUR YEARS.

THE 1983 BUDGET WILL ENABLE US TO ADD SOME 4,914 NEW AND COMPETING RENEWAL GRANTS TO THE GRANTS CONTINUING FROM PREVIOUS YEARS SO THAT DURING 1983 WE WILL BE SUPPORTING A TOTAL OF ABOUT 16,357 INVESTIGATOR-INITIATED PROJECTS.

AT THE SAME TIME WE ARE ALSO SUPPORTING SOME 9,969 RESEARCH TRAINEES. TO ACHIEVE THOSE LEVELS FOR RESEARCH AND TRAINING GRANTS, HOWEVER, WE HAVE HAD TO SHIFT FUNDS FROM OTHER SUPPORT PROGRAMS, MOST NOTABLY CLINICAL TRIALS AND INITIATIVES, TO EMPHASIZE SPECIAL AREAS SUCH AS RESEARCH CENTERS.

HOWEVER, GIVEN FINITE RESOURCES AND A COMMITMENT TO STABILIZATION OF ONE GROWING ELEMENT AMONG SEVERAL NECESSARY ACTIVITIES, THE ULTIMATE RESULT IS DE-STABILIZATION OF THE OTHERS. IN FACT, IF THE CURRENT RATE OF INCREASE IN THE PERCENTAGE OF THE NIH BUDGET DEVOTED TO THE EXTRAMURAL GRANT COMPONENT WERE TO CONTINUE, IT WOULD REACH 100 PERCENT AND PUSH ASIDE ALL OTHER ACTIVITIES BY AROUND 1993. OF COURSE, WE CANNOT PERMIT THAT TO HAPPEN.

THE FISCAL 1984 BUDGET IS STILL BEING NEGOTIATED WITH OMB. WITHOUT ADDITIONAL BUDGETARY SHIFTS AMONG NIH PROGRAMS, THE PRESIDENT'S BUDGET WOULD SUPPORT 3,676 COMPETING AWARDS AND 9,105 TRAINEES. IF, IN ADDITION, WE ARE REQUIRED TO PAY FULL INDIRECT COSTS, WE WILL BE ABLE TO SUPPORT ONLY ABOUT 3100 COMPETING AWARDS.

(SLIDE 6)

IN 1982 WE WERE ABLE TO FUND ONLY ABOUT 33 PERCENT OF APPROVED GRANT APPLICATIONS. THE 1983 BUDGET WOULD ENABLE US TO FUND ABOUT THE SAME PER-CENTAGE. THE PROJECTED 1984 BUDGET WOULD PROBABLY COVER ONLY ABOUT 25 PERCENT OF APPROVED APPLICATIONS. AT EITHER LEVEL WE ARE FAILING TO SUPPORT MUCH POTENTIALLY VALUABLE RESEARCH. THE COMPETITION IS INTENSE, AND PREDICTABLY GIVES RISE TO A CERTAIN AMOUNT OF GALLOWS' HUMOR. ONE STORY SUGGESTED BY THE CURRENT SITUATION GOES LIKE THIS: TWO FRIENDS ARE CAMPING IN GLACIER NATIONAL PARK. IN THE MORNING THEY START OUT ON A HIKE AND ALMOST IMMEDIATELY ENCOUNTER A FEROCIOUS GRIZZLY BEAR. THEY RUN BACK TO THE TENT, WHERE ONE HIKER FRANTI-CALLY PULLS OFF HIS HIKING BOOTS AND PUTS ON HIS RUNNING SHOES. HIS FRIEND ASKS, "WHY ARE YOU DOING THAT? YOU CAN'T OUTRUN A BEAR." THE FIRST HIKER REPLIED, "I DON'T HAVE TO OUTRUN THE BEAR - I ONLY HAVE TO OUTRUN YOU."

WE EXPECT PRESSURES TO INTENSIFY IN THE FUTURE BECAUSE OF SOME TRENDS OVER WHICH WE HAVE LITTLE OR NO CONTROL. FOR EXAMPLE, THE AVERAGE COST PER GRANT HAS GROWN FASTER THAN THE RATE OF INFLATION, AND INDIRECT COSTS HAVE INCREASED FASTER THAN DIRECT COSTS.

(SLIDES 7 and 8)

BETWEEN 1971 AND 1981, DIRECT COSTS GREW BY A FACTOR OF 3.6 BUT INDIRECT COSTS INCREASED ALMOST FIVEFOLD. THE CLEAREST ILLUSTRATION OF THIS DIFFERENTIAL OCCURRED IN 1982. OF $76 MILLION ADDITIONAL FUNDING FOR RESEARCH GRANTS OVER THE PREVIOUS YEAR, $34 MILLION OR 46 PERCENT WENT TO INDIRECT COSTS.

THE DILEMMA FOR US IS HOW TO ENSURE THAT ALL ESSENTIAL AND VITAL ACTIVITIES ARE CONTINUED WHILE WE MAINTAIN STABILITY IN THE RESEARCH AND TRAINING BASE. MANY OF OUR INSTITUTE DIRECTORS FEEL THAT FURTHER SHIFTS TO MAINTAIN THE LEVEL OF NEW AND COMPETING GRANTS WOULD SERIOUSLY LIMIT THEIR ABILITY TO MEET OTHER GOALS AND TO ASSURE NECESSARY PROGRAM BALANCE.

THIS YEAR WE HAVE ASKED THE DIRECTOR'S ADVISORY COMMITTEE TO PARTICIPATE IN A REVIEW OF THE IMPACT OF OUR STABILIZATION POLICY ON ALL OF NIH AND PARTICULARLY THE EXTRAMURAL PROGRAMS. WE WILL ANALYZE THE FACTORS CONTRIBUTING TO THE INCREASING COSTS OF RESEARCH PROJECTS, INCLUDING INDIRECT COSTS AND FACULTY SALARY SUPPORT WITH A VIEW TO ACHIEVING GREATER EFFICIENCY IN THE SUPPORT OF RESEARCH. BUT I AM CONVINCED THAT, EVEN AFTER CAREFUL REVIEW, THE CONCEPT OF STABILIZATION WILL BE REAFFIRMED AS A POLICY, THOUGH PERHAPS IN MODIFIED FORM.

LAST WEEK I SPOKE TO THE COUNCIL OF ACADEMIC SOCIETIES WHICH IS MADE UP OF REPRESENTATIVES OF THE MANY FACETS OF MEDICAL EDUCATION AND THE RELATED SCIENTIFIC DISCIPLINES. I TOLD THEM MANY OF THE THINGS I HAVE MENTIONED HERE AND, IN THE DISCUSSION, SUGGESTED THAT WE JOINTLY EXPLORE WAYS IN WHICH THE ADMINISTRATIVE COSTS INCIDENT TO OUR JOINT RESEARCH EFFORTS MIGHT BE REDUCED. AS AN EXAMPLE, WE DISCUSSED CERTAIN INCREASING OVERHEAD COSTS INVOLVED IN THE PREPARATION AND REVIEW OF GRANT APPLICATIONS. MEMBERS OF THIS AUDIENCE WHO HAVE ENGAGED IN THE STIMULATING TASK OF PREPARING GRANT APPLICATIONS MAY BE INTERESTED IN SOME OF THE INFORMATION PRODUCED IN A RECENT STUDY BY OUR DIVISION OF RESEARCH GRANTS. BETWEEN 1981 AND 1982 THE NUMBER OF COMPETING APPLICATIONS ROSE FROM 15,732 TO 16,989. THE LATTER TOTAL WAS ALMOST DOUBLE THE 8600 APPLICATIONS RECEIVED IN 1972.

EVEN MORE SURPRISING IS THE FACT THAT LAST YEAR ONE-FOURTH OF ALL APPLICATIONS WERE RESUBMISSIONS--A CATEGORY OF APPLICATIONS THAT HAS DOUBLED IN SIZE IN THE PAST THREE TO FIVE YEARS.

ADDITIONALLY, THERE APPEARS TO BE A TREND TOWARD MULTIPLE APPLICATIONS PER INVESTIGATOR AND A FLOODING OF THE MARKET BY SOME SCHOOLS. A LARGE NUMBER OF SUBMISSIONS FROM A GIVEN INSTITUTION OR INDIVIDUAL DOES NOT NECESSARILY CORRELATE WITH AN INCREASED NUMBER OF AWARDS. IN FACT, AMONG MAJOR RESEARCH-ORIENTED MEDICAL SCHOOLS IN 1981, THE INSTITUTION WHOSE FACULTY SUBMITTED THE SMALLEST NUMBER OF APPLICATIONS (155) WAS AWARDED THE LARGEST NUMBER OF GRANTS (83). WHILE WE DID NOT SUGGEST TO THE COUNCIL OF ACADEMIC SOCIETIES THAT THERE

BE ANY RESTRICTION ON GOOD IDEAS, WE DID SUGGEST THAT A GREATER MEASURE OF QUALITY CONTROL IN PREPARATION AND SUBMISSION OF GRANT APPLICATIONS AT THE INSTITUTIONAL LEVEL COULD SAVE TIME AND EXPENSE FOR THE FACULTY, OUR DIVISION OF RESEARCH GRANTS, AND THE STUDY SECTION REVIEWERS.

PERMIT ME TO TURN NOW TO ANOTHER JOINT CONCERN; NAMELY, THE TRAINING OF INVESTIGATORS TO MAINTAIN THE VITALITY OF RESEARCH.

THE CONCERNS HERE GO BEYOND THE OVERALL NUMBER OF TRAINEES. FOR EXAMPLE, ALTHOUGH THERE IS CURRENTLY AN ADEQUATE SUPPLY OF SCIENTISTS IN MOST FIELDS, THE PROPORTION OF PHYSICIANS APPLYING FOR SUPPORT TO PERFORM CLINICAL RESEARCH IS DECLINING. THE SITUATION IS COMPOUNDED BY THE FACT THAT THE SUCCESS RATE AMONG PHYSICIAN APPLICANTS FOR GRANTS IS NOW LOWER THAN THE SUCCESS RATE FOR PH.D.s OR FOR THE RELATIVELY SMALL NUMBER OF APPLICANTS HOLDING THE COMBINED M.D./PH.D. DEGREES.

(SLIDES 9)

IT SEEMS CLEAR THAT INCREASINGLY TRAINING AND EXPERIENCE IN THE METHODOLOGY OF RESEARCH IS A DISTINCT ADVANTAGE FOR THE APPLICANT.

(SLIDE 10)

BUT FEWER PHYSICIANS TODAY ARE INTERESTED IN TRAINING THEMSELVES AS RESEARCHERS. OF THE 2800 POSITIONS THAT THE NATIONAL ACADEMY OF SCIENCES RECOMMENDS THAT THE NIH DEVOTE TO CLINICAL TRAINING, APPROXIMATELY 900 ARE NOW FILLED BY PH.D.s, COMPARED WITH ONLY 450 SEVERAL YEARS AGO. ONLY 1900 ARE FILLED BY M.D.s.

WHAT ARE THE MAJOR BARRIERS TO ATTRACTING MORE M.D.s INTO RESEARCH?

APPARENTLY ONE SUCH BARRIER IS THEIR PERCEPTION OF INSTABILITY IN THE SUPPORT OF RESEARCH. ANOTHER IS THE INCREASING COMPLEXITY OF SCIENCES WHICH IMPLIES A NEED FOR LONGER PERIODS OF TRAINING AND THUS AN INCREASE IN THE ALREADY HEAVY DEBT LOAD INCURRED BY PHYSICIANS. THERE IS A SHARP DIFFERENTIAL IN THE STIPENDS PAID DURING TRAINING, WITH THE ANNUAL STIPEND FOR RESEARCH TRAINEES SOME $5000 LESS THAN THE EQUIVALENT RESIDENCY POSITION IN A HOSPITAL.

SOME APPROACHES TO LOWERING THESE BARRIERS INCLUDE EARLIER EXPOSURE OF STUDENTS TO RESEARCH EXPERIENCES; GREATER FLEXIBILITY IN MEDICAL CURRICULA (DUKE IS A LEADER HERE), GRADUATE TRAINING AND BOARD REQUIREMENTS; A REALIZATION AMONG RESEARCHERS AND TRAINEES THAT A SUBSTANTIAL PERIOD OF TRAINING IS REQUIRED; AND,

VERY IMPORTANTLY, AN ASSURANCE BY FEDERAL AGENCIES OF BOTH STABILITY AND ACCESS TO THE SYSTEM OF RESEARCH SUPPORT BY YOUNG INVESTIGATORS.

AN INCREASE IN THE PHYSICIAN'S STIPEND MIGHT ATTRACT M.D.s INTO RESEARCH TRAINING, BUT GIVEN A LIMITED BUDGET, THIS WOULD FORCE A REDUCTION IN NUMBER OF TRAINEES. OUR DILEMMA IS HOW TO MAINTAIN THE ESSENTIAL SUPPORT LEVEL FOR NON-CLINICAL TRAINEES WHILE FINDING INCENTIVES TO ENCOURAGE MORE PHYSICIANS TO ENTER RESEARCH.

AS A PARTIAL SOLUTION TO THIS PROBLEM, WE ARE CURRENTLY CONSIDERING A NEW TYPE OF TRAINING PROGRAM, PERHAPS TO BE CALLED A PHYSICIAN-INVESTIGATOR DEVELOPMENT PROGRAM, WHICH WOULD PROVIDE SUPPORT FOR THREE TO FIVE YEARS OF FULL-TIME RESEARCH TRAINING WITH A STIPEND ABOVE THE RESIDENCY LEVEL AND WOULD INCLUDE GRADUATE COURSE WORK. THESE TRAINING PROGRAMS WOULD BE BASED IN DEPARTMENTS WITH ESTABLISHED RECORDS IN PRODUCING PHYSICIAN-SCIENTISTS. THE NEW PROGRAM WOULD NOT REPLACE CURRENT TRAINING OR FELLOWSHIP PROGRAMS AND WOULD BE SMALLER IN SCALE, PERHAPS LEVELING OFF AT ABOUT 400 TRAINEES IN THREE YEARS. ITS GOAL WOULD BE TO RAISE THE TOTAL NUMBER OF M.D. RESEARCH TRAINEES FROM THE PRESENT LEVEL OF 1900 TO ABOUT 2300 PER YEAR.

LET ME MENTION ANOTHER MATTER WHICH IS OF DIRECT CONCERN TO THE NIH, BUT BECAUSE IT CAN AFFECT THE ADMINISTRATIVE EFFICIENCY OF THE AGENCY IS OF MORE THAN PASSING INTEREST TO ACADEMIC INSTITUTIONS AS WELL.

WITH GROWING PUBLIC AWARENESS OF THE POTENTIAL FOR SUCCESSFUL INTERVENTION IN DISEASE PROCESSES, WE CAN EXPECT CONTINUED PRESSURE FOR ADDITIONAL, NARROWLY FOCUSED RESEARCH EFFORTS. IN RECENT YEARS, FOR EXAMPLE, THERE HAVE BEEN TEN PROPOSALS FOR NEW INSTITUTES AND FIVE TRANSFERS.

(SLIDES 11 and 12)

IN MY OPINION, ADDITIONAL CATEGORICAL, DISEASE SPECIFIC INSTITUTES AT THE NIH WOULD NOT CONTRIBUTE TO THE MOST EFFICIENT ADMINISTRATION OF RESEARCH AND WOULD ONLY LEAD TO INCREASED ADMINISTRATIVE COSTS AT THE EXPENSE OF FUNDING FOR RESEARCH.

I AM MINDFUL OF THE HISTORY OF THE DEVELOPMENT OF THE FEDERAL BIOMEDICAL RESEARCH ENTERPRISE AND AWARE THAT THE IMPETUS FOR ITS RAPID GROWTH OFTEN CAME FROM JUST SUCH NARROW PRESSURES AS WE ARE CURRENTLY EXPERIENCING. THE NAMES OF THE CONSTITUENT INSTITUTES OF THE NIH STAND AS STATEMENTS OF THE POWER OF PUBLIC CONCERN ABOUT SPECIFIC DISEASES AND FAMILIES OF DISORDERS.

BUT THE NATURE OF RESEARCH HAS CHANGED. ARTHUR KORNBERG, NOBEL LAUREATE AND MEMBER OF THE NIH DIRECTOR'S ADVISORY COMMITTEE, HAS WRITTEN OF A "PROFOUND

DEVELOPMENT IN MEDICAL SCIENCE" REFERRING TO THE "CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SCIENCE SUBJECTS INTO A SINGLE, UNIFIED DISCIPLINE. ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY, AND GENETICS HAVE NOW MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY." SINCE BIOMEDICAL SCIENCE FOCUSES INCREASINGLY ON FUNDAMENTAL PROCESSES OF LIFE AND INTERRELATIONSHIPS AMONG DISEASE ENTITIES, CREATION OF ADDITIONAL CATEGORICAL DISEASE-SPECIFIC INSTITUTES IS NOT IN OUR JUDGMENT THE MOST EFFICIENT WAY TO EMPLOY NATIONAL RESOURCES FOR THE SUPPORT OF RESEARCH.

BUT HOW CAN NIH BEST SUPPORT AND MANAGE THE CONTINUING EVOLUTION OF THE HEALTH SCIENCES FOR MAXIMUM PUBLIC BENEFIT?

TO HELP RESOLVE QUESTIONS OF NIH ORGANIZATION, WE HAVE ASKED THE INSTITUTE OF MEDICINE TO MAKE AN EIGHTEEN-MONTH STUDY OF THE PRESENT STRUCTURE, TO EXAMINE ITS ADEQUANCY AND EFFICIENCY, AND TO DEVISE CRITERIA BY WHICH WE CAN EVALUATE AND DETERMINE NEED FOR FUTURE CHANGE.

SEVERAL ISSUES OF CONCERN TO THE NIH AND ACADEMIC INSTITUTIONS ALIKE ARE LIKELY TO BE ADDRESSED BY THE NEW 98TH CONGRESS. THESE INCLUDE PROPOSALS TO ESTABLISH ADDITIONAL INSTITUTES, REAUTHORIZATION OF SEVERAL NIH PROGRAMS, LEGISLATION INVOLVING THE USE OF ANIMALS IN RESEARCH AND TESTING, INDIRECT COST REIMBURSEMENTS, MISCONDUCT IN SCIENCE, ETHICAL ASPECTS OF GENETIC ENGINEERING, AND COMMERCIALIZATION OF RESEARCH. ALL DESERVE THE MOST CAREFUL CONSIDERATION. EACH OF US HAS THE RESPONSIBILITY TO RESPOND IN TERMS OF THE LONG-RANGE PERSPECTIVE OF A SCIENCE WHOSE ULTIMATE OBJECTIVE IS TO IMPROVE HUMAN HEALTH.

IN CONCLUSION, I WILL VENTURE A LOOK AT THE FUTURE AND IDENTIFY A FEW OF THE ISSUES THAT I BELIEVE TO BE MOST SIGNIFICANT FOR THE CONTINUED SUCCESS OF THE FEDERAL-ACADEMIC PARTNERSHIP.

FOREMOST IS THE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR THE RESEARCH ENTERPRISE. I MENTIONED EARLIER THAT CURRENTLY WE ARE ABLE TO AWARD ONLY 30-35 PERCENT OF THE APPROVED APPLICATIONS FOR RESEARCH SUPPORT. WE BELIEVE THE OPTIMAL LEVEL FOR PROGRESS IS 45 TO 50 PERCENT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. TO ACHIEVE SUCH A GOAL, WE WOULD NEED AN ADDITIONAL $300-$400 MILLION PER YEAR FOR THREE YEARS, AND THEREAFTER AN ANNUAL BUDGET OF $5 BILLION ADJUSTED FOR INFLATION.

ANOTHER PROBLEM IS THE NEED TO REPLACE OR PURCHASE INCREASINGLY SOPHISTICATED RESEARCH INSTRUMENTS. IT IS ESTIMATED THAT $20 MILLION A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED-INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969. WE NEED TO HELP MODERNIZE AND TO CONSTRUCT NEW LABORATORIES.

I WANT TO EMPHASIZE THAT IT IS NOT POSSIBLE TO ACCOMPLISH THESE GOALS IMMEDIATELY. GIVEN THE STATE OF THE ECONOMY, NIH HAS FARED WELL. OUR BUDGET REPRESENTS A STRONG COMMITMENT BY THE ADMINISTRATION TO BIOMEDICAL RESEARCH. BUT I BELIEVE THAT AS THE ECONOMY IMPROVES, IT IS IMPERATIVE TO INCREASE THAT LEVEL OF SUPPORT.

ANY DISCUSSION OF THE FUTURE OF THE FEDERAL-ACADEMIC PARTNERSHIP WOULD BE INCOMPLETE WITHOUT MENTION OF A NEW SET OF RESEARCH RELATIONSHIPS DEVELOPING BETWEEN UNIVERSITIES AND INDUSTRY. I SPOKE RECENTLY AT A CONFERENCE DEVOTED TO AN EXAMINATION OF THE THREE-WAY RELATIONSHIP INVOLVING ACADEMIA, INDUSTRY, AND GOVERNMENT IN THE CONDUCT OF RESEARCH.

AS YOU KNOW, VOICES FROM THE SCIENTIFIC COMMUNITY AND ELSEWHERE HAVE EXPRESSED A WIDE VARIETY OF OPINIONS ABOUT THE DESIRABILITY OF THE NEW RELATIONSHIP RANGING FROM PREDICTIONS THAT IT WILL LEAD TO EROSION OF ACADEMIC VALUES TO FORECASTS THAT IT WILL BE A PANACEA FOR OUR FINANCIAL TROUBLES. SOME OF THESE EXPRESSIONS REMINDED ME OF POPULAR DESCRIPTIONS OF THE BERMUDA TRIANGLE WHERE IT IS SAID THERE IS A MYSTERIOUS FORCE FIELD THAT SWALLOWS UP THOSE WHO ENTER. SOME OF THE ISSUES RAISED BY THE NEW UNIVERSITY-CORPORATE ARRANGEMENTS FOR RESEARCH ARE AS MYTHICAL AS THE BERMUDA TRIANGLE, WHILE OTHERS ARE REAL AND STILL OTHERS ARE OF AMBIGUOUS POTENTIAL. THE ISSUES AND PROBLEMS ARE PRIMARILY AT THE INTERFACE BETWEEN ACADEMIA AND THE CORPORATE WORLD. THERE HAVE BEEN SUGGESTIONS THAT THE NIH TAKE A LEADERSHIP ROLE TO ASSURE THAT THE ACCOMMODATION OF THE NEW PARTNER DOES NOT ADVERSELY AFFECT THE RESEARCH ENTERPRISE. WE HAVE NOT DONE SO. WE BELIEVE IT PREFERABLE THAT THESE NEW RELATIONSHIPS EVOLVE AS THEY HAVE WITH THE GOVERNMENT PLAYING A FACILITATIVE ROLE.

SOME YEARS AGO, CLARK KERR IN HIS BOOK ON "THE USES OF THE UNIVERSITY," COMMENTED THAT "TWO GREAT IMPACTS, BEYOND ALL OTHER FORCES, HAVE MOLDED THE MODERN AMERICAN UNIVERSITY SYSTEM AND MADE IT DISTINCTIVE. BOTH IMPACTS HAVE COME FROM SOURCES OUTSIDE THE UNIVERSITY. BOTH HAVE COME FROM THE FEDERAL GOVERNMENT. BOTH HAVE COME IN RESPONSE TO NATIONAL NEED. THE FIRST WAS THE LAND-GRANT MOVEMENT. THE SECOND GREAT IMPACT ON THE UNIVERSITIES BEGAN WITH FEDERAL SUPPORT OF SCIENTIFIC RESEARCH DURING WORLD WAR II."

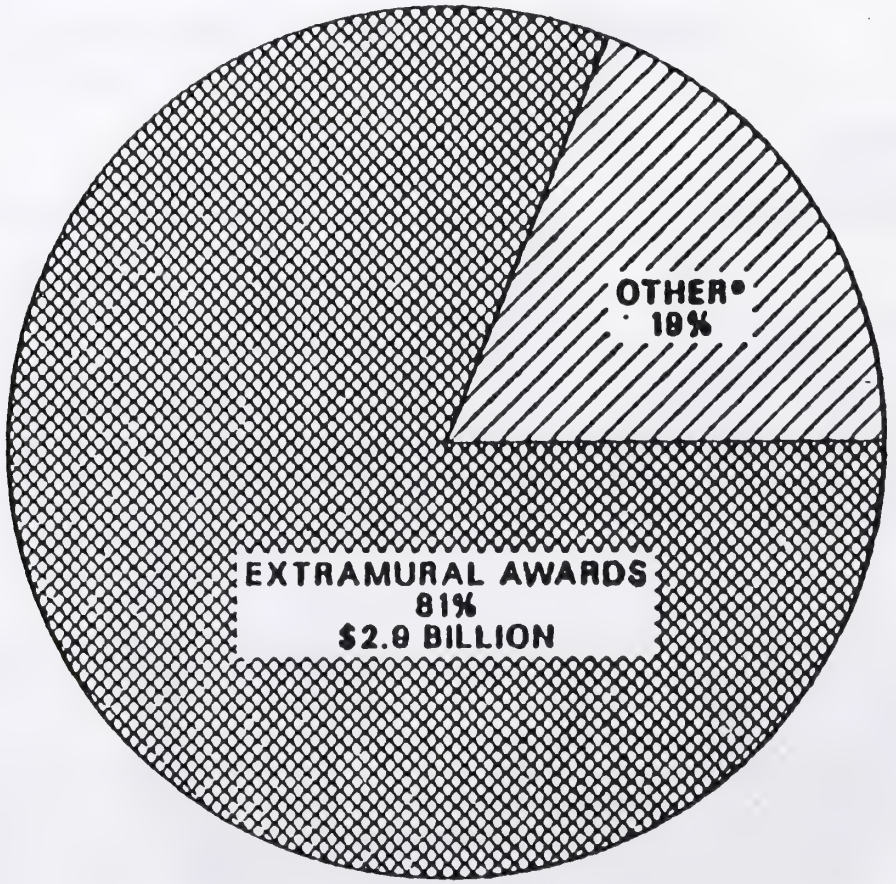
IN THE FIELD OF BIOMEDICAL RESEARCH THE IMPACT OF THE SECOND EVENT HAS EXTENDED FAR BEYOND THE UNIVERSITY, AND THE BENEFITS OF THE FEDERAL ACADEMIC PARTNERSHIP HAVE PROVIDED THE MEANS FOR IMPROVEMENT IN THE QUALITY OF LIFE FOR PEOPLE THROUGHOUT THE WORLD.

* * *

SLIDE 1

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET

FISCAL YEAR 1982



TOTAL - $3.6 BILLION

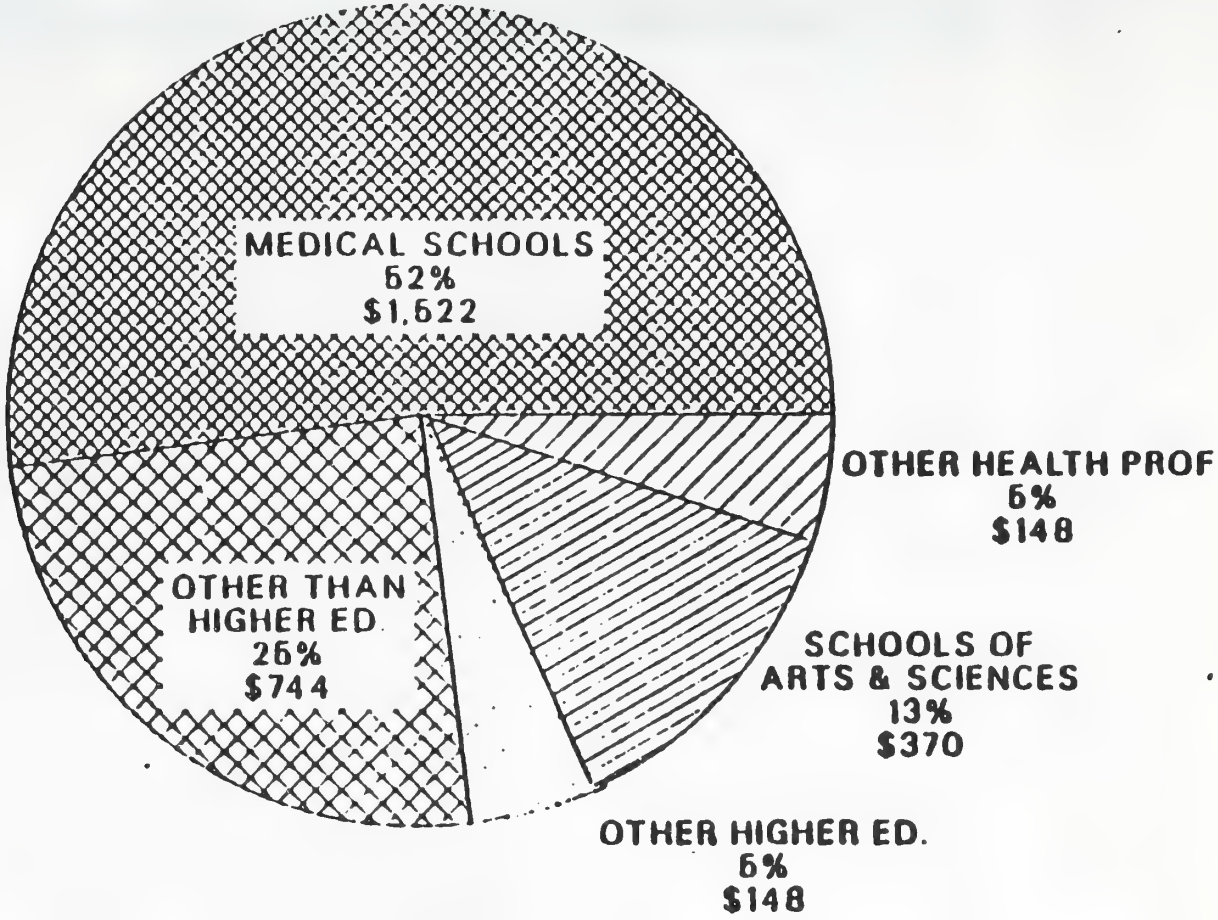
*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

LIDE 2

MEDICAL SCHOOLS RECEIVE 52% OF ALL NIH AWARDS, FISCAL YEAR 1982

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



FY 1982*

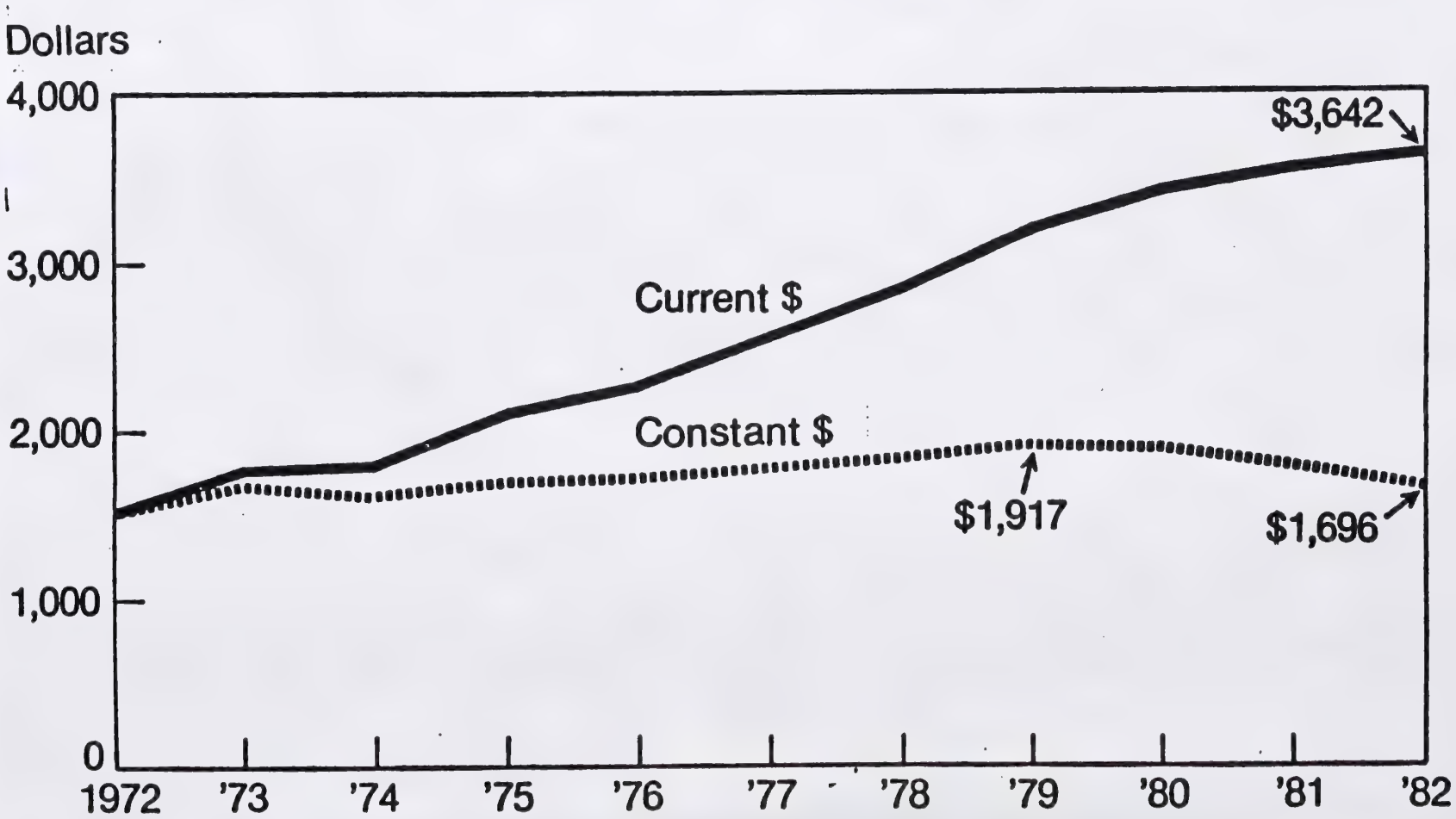
$2,933 MILLION

*PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

IDE 3

Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)



TRENDS IN HIGHER EDUCATION FACULTY SALARIES 1972-1982
CURRENT DOLLARS
CONSTANT DOLLARS
PROFESSOR
ASSOCIATE
ASSISTANT
INSTRUCTOR
OTHER
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
$35,000
$40,000
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982

SLIDE 4

SLIDE 5

ALLOCATION OF FEDERAL AWARDS BY ACTIVITY (FISCAL YEARS 1972-1982)
(PERCENT OF AMOUNT/CURRENT DOLLARS IN MILLIONS)
PRESENT PLAN
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
$24,000
$26,000
$28,000
$30,000
$32,000
$34,000
$36,000
$38,000
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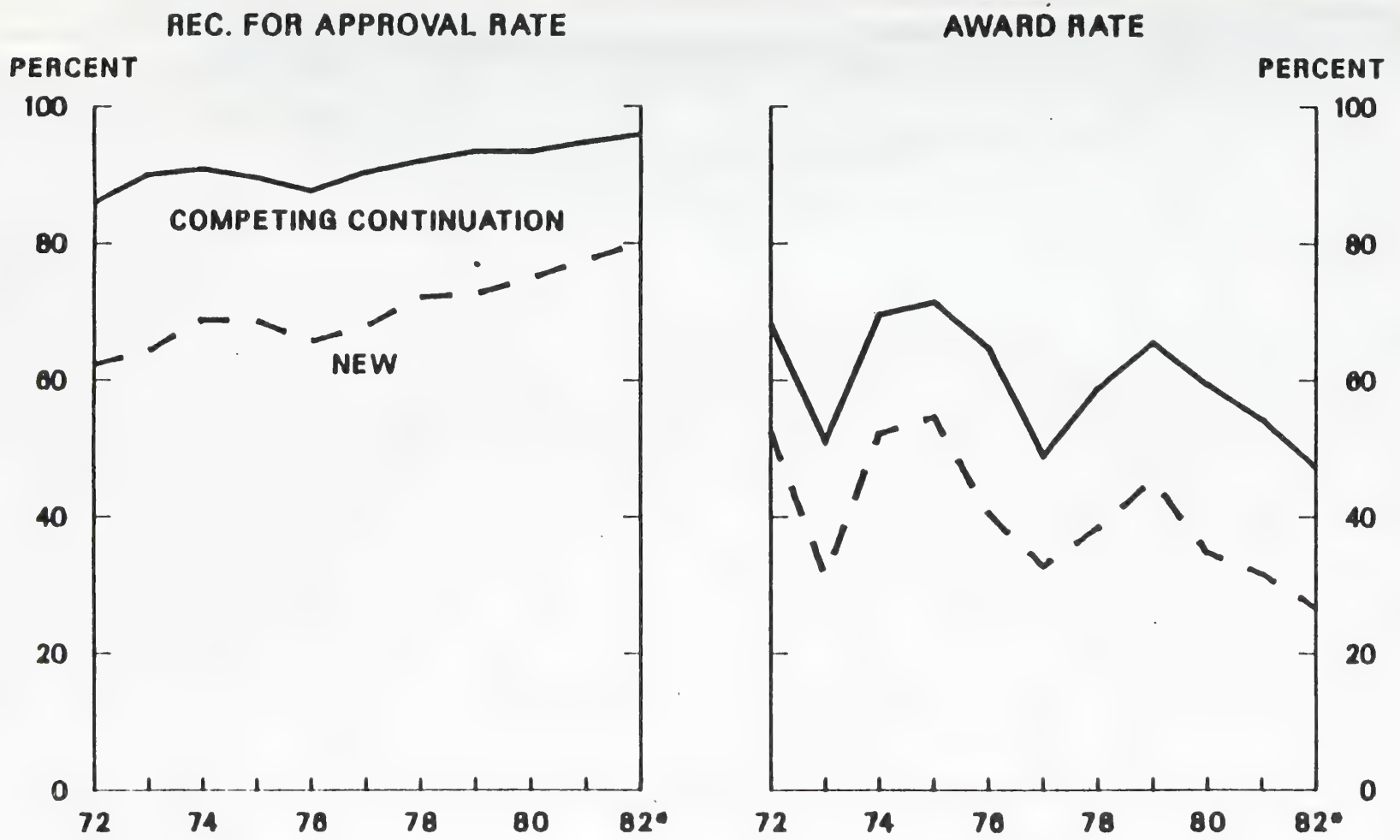
SLIDE 6

COUNCIL RECOMMENDED FOR APPROVAL AND AWARD RATES FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS BY TYPE, FISCAL YEAR 1972-1982



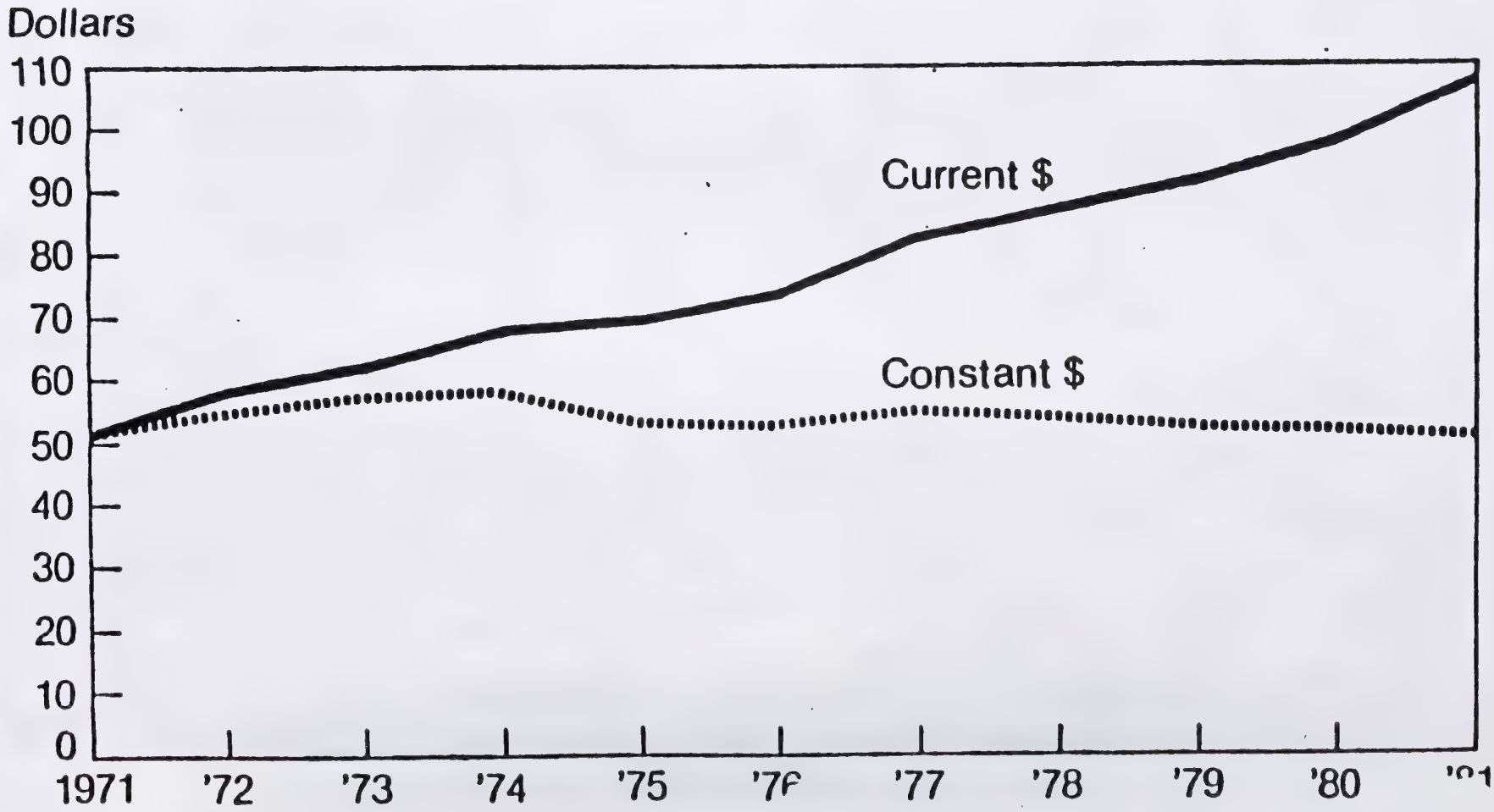
NOTE: DATA BASED ON NIH STANDARD PROCEDURES. *PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

SLIDE 7

SLIDE 7

Average Research Project Grant, 1971-81

In Current and Constant Dollars (Thousands)



INDIRECT COST PERCENTAGE OF TOTAL COST FOR NIH RESEARCH GRANTS

FISCAL YEARS 1972-1982

26%

24

22

20

18

16

14

12

10

8

6

4

2

0

1972 73 74 75 76 77 78 79 80 81 82

SOURCE: NIH ANALYSIS BASED ON DATA FROM DEPARTMENT OF HEALTH AND HUMAN SERVICES

PREPARED BY THE COMMITTEE ON SCIENCE AND TECHNOLOGY

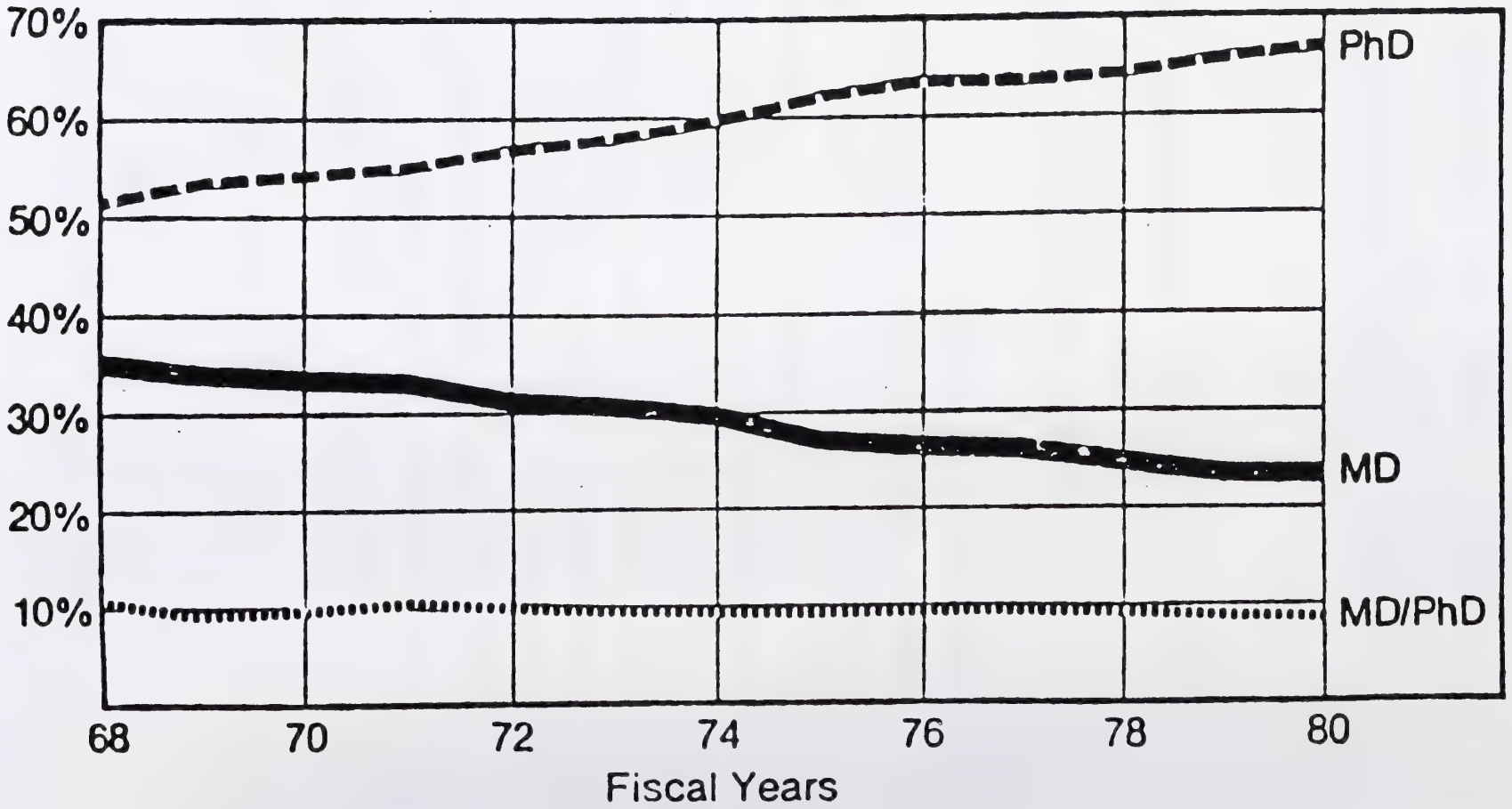
SCALE 8

SLIDE 10

Percentage of M[illegible] Postdoctoral Trainees and Fellows

SLIDE 9

P.I.'s Holding MD, PhD or MD/PhD Degrees As a Percentage of All P.I.'s on R01 Grants



PROGRAM AND POLICY DIRECTIONS OF THE NATIONAL INSTITUTES OF HEALTH*

By

James B. Wyngaarden, M.D.**

I APPRECIATE THIS OPPORTUNITY TO DISCUSS PROGRAM AND POLICY DIRECTIONS OF THE NATIONAL INSTITUTES OF HEALTH WITH THOSE OF YOU REPRESENTING ACADEMIC VETERINARY MEDICINE. ALTHOUGH IT IS RELATIVELY SMALL, THE COMMUNITY WHICH YOU REPRESENT IS AN ESSENTIAL PART OF OUR NATION'S BIOMEDICAL RESEARCH ENTERPRISE. THE SCIENTIFIC FACULTIES IN YOUR COLLEGES ARE IMPORTANT MEMBERS OF THE FEDERAL ACADEMIC PARTNERSHIP IN BIOMEDICAL RESEARCH THAT HAS FUNCTIONED SO EFFECTIVELY SINCE THE 1940's. THERE ARE A NUMBER OF SERIOUS PROBLEMS IN THE CONDUCT AND SUPPORT OF BIOMEDICAL RESEARCH THAT WE WILL NEED TO ADDRESS IN A COLLEGIAL MANNER. WE ARE VERY MUCH TOGETHER IN THIS EFFORT, AS A FEW STATISTICS WILL INDICATE.

THE FEDERAL GOVERNMENT SUPPORTS AN ESTIMATED 90 PERCENT OF BASIC BIOMEDICAL RESEARCH IN THIS COUNTRY AND MORE THAN 60 PERCENT OF BIOMEDICAL RESEARCH AND DEVELOPMENT AT

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* Remarks at a meeting the Association of American Veterinary Medical Colleges, Hyatt Regency Crystal City, Arlington, Virginia, March 2, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

AMERICAN UNIVERSITIES AND MEDICAL SCHOOLS IS FUNDED BY NIH. EXTRAMURAL AWARDS IN FISCAL YEAR 1982 ACCOUNTED FOR 81 PERCENT OF THE NIH BUDGET OF 3.6 BILLION (SLIDE 1), AND 52 PERCENT OF AWARDS WENT TO MEDICAL SCHOOLS (SLIDE 2). FOLLOWING THE PATTERN OF RECENT YEARS, APPROXIMATELY ONE PERCENT WENT TO SCHOOLS OF VETERINARY MEDICINE, A PROPORTION WHICH I SUSPECT REFLECTS AN UNREALIZED POTENTIAL. IN ADDITION, THIS FIGURE DOES NOT INCLUDE A SUBSTANTIAL AMOUNT OF COMPARATIVE BIOMEDICAL RESEARCH CARRIED OUT IN MEDICAL SCHOOLS AND OTHER INSTITUTIONS WITH SIGNIFICANT INVOLVEMENT FROM THE VETERINARY PROFESSION. IN FACT I WAS INTERESTED IN LEARNING, FROM A RECENT NATIONAL ACADEMY OF SCIENCES REPORT ON "SPECIALIZED VETERINARY MANPOWER NEEDS THROUGH 1990," THAT THE NUMBER OF DOCTORS OF VETERINARY MEDICINE ON THE FACULTIES OF MEDICAL SCHOOLS IS NOW MORE THAN 400, WHICH IS NEARLY A QUARTER OF THE NUMBER OF VETERINARIANS ON THE FACULTIES OF SCHOOLS OF VETERINARY MEDICINE.

THE NUMBER OF NIH GRANTS MADE TO VETERINARY SCHOOLS APPEARS TO BE RELATIVELY SMALL BECAUSE THE NUMBER OF APPLICATIONS RECEIVED FROM THOSE SCHOOLS IS ALSO SMALL. THOSE THAT ARE SUBMITTED GENERALLY COMPETE AS WELL AS APPLICATIONS FROM ANY OTHER GROUP. OF COURSE, ANOTHER FACTOR THAT MAY BE IMPORTANT IN THIS EQUATION IS THE SUPPORT RECEIVED BY YOUR COLLEGES FROM OTHER SECTORS, MOST NOTABLY AGRICULTURE.

EACH STEP IN THE GROWTH OF OUR RESEARCH ENTERPRISE HAS BEEN IN RESPONSE TO A UNIQUE SET OF CIRCUMSTANCES CREATED BY THE EVOLUTION OF SCIENCE, TECHNOLOGICAL DEVELOPMENTS, THE CHANGING EXPECTATIONS AND PRIORITIES OF THE PUBLIC AS EXPRESSED BY THE ADMINISTRATION AND CONGRESS, AND BY ECONOMIC CONDITIONS. MOST RECENTLY IT HAS BEEN THE COMBINATION OF ECONOMIC CONDITIONS AND CHANGING PUBLIC PERCEPTION THAT HAS HAD THE GREATEST INFLUENCE ON OUR ACTIVITIES.

BUDGET

A LOOK AT HOW OUR BUDGET HAS CHANGED DURING THE LAST 25 YEARS IS INSTRUCTIVE IN THAT REGARD. NIH'S MAIN PROGRAM GROWTH CAME DURING THE DECADE 1955-1965, WITH APPROPRIATIONS GROWING ROUGHLY FOURTEEN FOLD. SLIDE 3 SHOWS THE NIH BUDGET IN BOTH CURRENT AND CONSTANT DOLLARS FROM 1972 TO 1982. BETWEEN 1972 AND 1982, THERE HAS BEEN A 15 PERCENT INCREASE IN CONSTANT DOLLARS, BUT THE GROWTH OF INDIRECT COSTS DURING THIS PERIOD HAS ALMOST EXACTLY CONSUMED THIS INCREMENT SO THAT THE FUNDS AVAILABLE TO SUPPORT THE DIRECT COSTS OF RESEARCH ARE ESSENTIALLY THE SAME IN 1983 AS IN 1972. OUR PEAK YEAR WAS ACTUALLY IN 1979. THE BUDGET FELL BY 12 PERCENT IN PURCHASING POWER BETWEEN 1979 AND 1982 AND ROSE BY 4 PERCENT IN 1983 FOR A

NET DECREASE OF 8 PERCENT. THE FISCAL YEAR 1984 BUDGET FOR NIH SUBMITTED TO CONGRESS BY THE PRESIDENT REQUESTS $4.077 BILLION. THAT WOULD BE A $73 MILLION, OR 1.8 PERCENT, INCREASE OVER FISCAL YEAR 1983, FOR WHICH AN INFLATIONARY RATE OF 5 PERCENT IS PREDICTED.

IN SHORT, THE NIH BUDGET HAS BEEN ESSENTIALLY IN A STEADY STATE FOR MORE THAN A DECADE, AND WE CANNOT EXPECT DRAMATIC INCREASES IN THE NEAR FUTURE, CERTAINLY NOT UNTIL THE NATIONAL ECONOMY IMPROVES. AT THE SAME TIME, BIOMEDICAL RESEARCH HAS RECEIVED STRONG SUPPORT FROM PRESENT AND PREVIOUS ADMINISTRATIONS AND CONGRESSES, AND THE NIH HAS FARED BETTER THAN MANY OTHER AGENCIES IN RECENT YEARS. THE IMPORTANCE OF THE NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH TO PUBLIC HEALTH IS WIDELY RECOGNIZED.

HISTORICALLY WE HAVE BEEN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET AND AN INCREASING NUMBER OF EXCELLENT RESEARCH PROPOSALS BY SHIFTING FUNDS AMONG MECHANISMS. THESE CHANGES BEGAN IN 1975 (SLIDE 4) BUT WERE NOT ARTICULATED AS A POLICY UNTIL FISCAL YEAR 1980 WHEN WE ASKED THE CONGRESS FOR SUFFICIENT FUNDS TO SUPPORT A MINIMUM OF 5,000 NEW AND COMPETING RESEARCH GRANTS AND 10,000 TRAINEES.

Policy and Program Issues

With that context in mind, I would like to consider some program and policy issues that face NIH and our partnership. Steady-state resources inevitably intensify competition for support in all areas for which NIH is responsible. In addition to extramural research project grants, these include centers, contracts, clinical trials, research instruments, and facilities, as well as the intramural programs and facilities at NIH. Since our fundamental mission is the improvement of health and well-being, we must also emphasize prevention of disease and disability and make a special effort to see that scientific discoveries are transferred to medical practice as quickly as appropriate.

In awareness of those multiple responsibilities and of fiscal constraints, we have placed the highest priority on these objectives:

- To sustain maximum stability in the investigator-initiated research project base.

- TO SUPPORT THE TRAINING OF AN OPTIMUM NUMBER OF NEW INVESTIGATORS TO ASSURE CONTINUITY OF HIGH-QUALITY RESEARCH IN THE FUTURE.

- TO ORGANIZE THE AGENCY FOR MAXIMUM EFFICIENCY IN SUPPORT OF MODERN BIOMEDICAL RESEARCH.

STABILIZATION OF RESEARCH GRANTS

WE CONTINUE TO EMPHASIZE STABILITY IN THE RESEARCH PROJECT BASE BECAUSE PURSUIT OF FUNDAMENTAL KNOWLEDGE IS THE FOUNDATION OF PROGRESS IN THE HEALTH SCIENCES AND INVESTIGATOR-INITIATED RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY. OUR OBJECTIVE IS TO PROVIDE A STEADY AND PREDICTABLE LEVEL OF RESEARCH PROJECT SUPPORT, ONE THAT OFFERS CONTINUITY TO ESTABLISHED INVESTIGATORS AND THEIR WORK, AND THAT ENCOURAGES NEW SCIENTISTS TO ENTER THE FIELD.

THE STABILIZATION POLICY HAS IN FACT DONE JUST THAT. WE HAVE BEEN ABLE TO DAMPEN LARGE FLUCTUATIONS IN SUPPORT OF NEW AND COMPETING RENEWAL AWARDS. IN 1981, WE SUPPORTED 5,140 GRANTS, AND IN 1982, 5,027 GRANTS.

THE 1983 BUDGET WILL ENABLE US TO SUPPORT SOME 4,914 NEW AND COMPETING RENEWAL GRANT AWARDS WHICH, ADDED TO THE CONTINUING GRANTS MOSTLY IN THEIR SECOND OR THIRD YEARS, MAKE UP A RESEARCH GRANT PORTFOLIO OF ABOUT 16,357. WE ARE ALSO SUPPORTING SOME 9,969 TRAINEES. TO ACHIEVE THAT LEVEL, HOWEVER, WE HAVE HAD TO SHIFT FUNDS FROM SOME MECHANISMS, MOST NOTABLY CLINICAL TRIALS AND INITIATIVES, TO EMPHASIZE SPECIAL AREAS OR ACTIVITIES, SUCH AS RESEARCH CENTERS. THE FISCAL YEAR 1984 BUDGET IS STILL BEING NEGOTIATED WITH OMB. WITHOUT ADDITIONAL BUDGETARY SHIFTS, THE PRESIDENT'S BUDGET WOULD SUPPORT 3,876 COMPETING AWARDS AND 9,105 TRAINEES.

THE DIFFICULTY OF SETTING PRIORITIES AMONG COMPETING DEMANDS CAN BE ILLUSTRATED BY EXAMINING THE CHANGING LEVEL OF SUPPORT IN VARIOUS MECHANISM CATEGORIES OVER THE PAST DECADE.

Given finite resources and a commitment to stability in one growing element among several necessary activities, the ultimate result is de-stabilization of the others. In fact (slide 5), if the current rate of increase in percent of NIH budget devoted to the extramural grant component were to continue, it would reach 100 percent around 1993. Obviously we could not permit that to happen.

Those pressures will intensify in the future because of some trends over which we have little or no control. For example, the average cost per grant has grown faster than the rate of inflation, and indirect costs have increased faster than direct costs (slide 6): between 1972 and 1982, direct costs increased by a factor of 3.6 and indirect costs rose almost fivefold. The clearest reflection of this differential occurred in fiscal year 1982. Of $76 million additional funds expended for research grants, $34 million, or 46 percent, went to indirect costs.

The dilemma is: how are we to ensure that all essential and vital activities are continued while stability in the research and training base is maintained? Many institute directors feel that further shifts would seriously limit their ability to meet other

PROGRAM GOALS AND TO MAINTAIN PROGRAM BALANCE. THIS YEAR WE ARE INVOLVING THE DIRECTOR'S ADVISORY COMMITTEE IN A REVIEW OF THE IMPACT OF OUR STABILIZATION POLICY ON ALL OF NIH AND PARTICULARLY ON THE EXTRAMURAL PROGRAM. WE WILL ALSO ANALYZE THE FACTORS CONTRIBUTING TO THE INCREASING COST OF RESEARCH PROJECTS, INCLUDING AN ANALYSIS OF INDIRECT COSTS AND OF FACULTY SALARY SUPPORT, WITH A VIEW TOWARD ACHIEVING GREATER EFFICIENCY IN THE SUPPORT OF RESEARCH. BUT I AM CONVINCED THAT, EVEN AFTER CAREFUL REVIEW, THE CONCEPT OF STABILIZATION WILL BE REAFFIRMED AS A POLICY, THOUGH PERHAPS REDEFINED.

THE ACADEMIC COMMUNITY MIGHT ALSO EXPLORE WAYS IN WHICH WE COULD BOTH REDUCE OVERHEAD COSTS IN THE PREPARATION AND REVIEW OF GRANT APPLICATIONS. BETWEEN 1981 AND 1982, FOR EXAMPLE, THE NUMBER OF COMPETING APPLICATIONS ROSE FROM 15,732 TO 16,989, THE LATTER TOTAL ALMOST DOUBLE THE 8,600 APPLICATIONS RECEIVED IN 1972. LAST YEAR, 25 PERCENT OF ALL APPLICATIONS WERE RE-SUBMISSIONS. THIS FIGURE IS TWICE THE NUMBER OF 3-5 YEARS AGO. ADDITIONALLY THERE APPEARS TO BE A TREND TOWARD MULTIPLE APPLICATIONS PER INVESTIGATOR AND A FLOODING OF THE MARKET BY SOME SCHOOLS. A LARGE NUMBER OF SUBMISSIONS DOES NOT NECESSARILY CORRELATE WITH AN INCREASED NUMBER OF AWARDS. IN FACT, IN A REVIEW OF APPLICATIONS FROM MAJOR RESEARCH-ORIENTED MEDICAL

SCHOOLS IN 1981, WE FOUND THAT THE UNIVERSITY WHOSE FACULTY SUBMITTED THE LEAST NUMBER OF APPLICATIONS (155) WAS AWARDED THE LARGEST NUMBER OF GRANTS (83). WHILE WE DO NOT SUGGEST THAT THERE BE ANY RESTRICTION ON GOOD IDEAS, WE DO SUGGEST THAT A GREATER MEASURE OF QUALITY CONTROL IN PREPARATION AND SUBMISSION OF GRANT APPLICATIONS AT THE INSTITUTIONAL LEVEL COULD SAVE TIME AND EXPENSE FOR THE FACULTY, THE DIVISION OF RESEARCH GRANTS, AND STUDY SECTION REVIEWERS.

TRAINING

ANOTHER CONTINUING ISSUE OF CONCERN IS THE TRAINING OF THE NEXT GENERATION OF SCIENTIFIC INVESTIGATORS WHO ARE ESSENTIAL TO THE CONTINUED VIGOR OF INQUIRY. NIH HAS SOUGHT TO PROVIDE STABLE SUPPORT FOR RESEARCH TRAINING PROGRAMS. AS I MENTIONED EARLIER, WE ARE SUPPORTING APPROXIMATELY 10,000 TRAINEE POSITIONS PER YEAR. WE ARE WORKING CLOSELY WITH THE NATIONAL ACADEMY OF SCIENCES TO IDENTIFY NEEDS AND MATCH THEM WITH OPPORTUNITIES IN SCIENCE. WE REALIZE IT IS DIFFICULT TO QUANTIFY SUCH ACTIVITY, BUT IT IS IMPORTANT TO REDUCE THE WIDE SWINGS EXPERIENCED IN THE PAST.

WHILE VETERINARIANS RECEIVE SUPPORT FROM THE VARIETY OF TRAINING PROGRAMS FUNDED BY ALL OF OUR INSTITUTES, ONE OF OUR TRAINING ACTIVITIES IS UNIQUE TO YOUR PROFESSION: (SLIDE 7) THE LABORATORY ANIMAL SCIENCE AND MEDICINE TRAINING SUPPORTED BY THE DIVISION OF RESEARCH RESOURCES ANIMAL RESOURCES PROGRAM. IN FISCAL YEAR 1982 THIS ACTIVITY FUNDED NINE INSTITUTIONAL TRAINING PROGRAMS WITH 31 TRAINEE POSITIONS AND TWO INDIVIDUAL POSTDOCTORAL FELLOWSHIPS. APPROXIMATELY 169 TRAINEES AND FELLOWS HAVE COMPLETED TRAINING SINCE INCEPTION OF THE TRAINING PROGRAM IN LABORATORY ANIMAL SCIENCE AND MEDICINE. MOST OF THESE INDIVIDUALS ARE CONTINUING THEIR CAREERS IN BIOMEDICAL RESEARCH. FIFTY-NINE ARE CURRENTLY EMPLOYED BY MEDICAL SCHOOLS, AND 64 ARE EMPLOYED BY OTHER ACADEMIC, RESEARCH, OR GOVERNMENT ORGANIZATIONS.

PERPHAPS OF PARTICULAR INTEREST TO YOU IS THE SPECIAL EMPHASIS RESEARCH CAREER AWARD IN LABORATORY ANIMAL SCIENCE OR SERCA PROGRAM, WHICH THE ANIMAL RESOURCES PROGRAM HAS DEVELOPED FOR VETERINARIANS (SLIDE 8).

THIS SPECIAL AWARD IS MADE TO DEVELOP MULTIDISCIPLINARY VETERINARY RESEARCHERS WHO WILL DIRECT THEIR RESEARCH TOWARD REFINING THE USE OF LABORATORY ANIMALS IN BIOMEDICAL RESEARCH, THE STUDY OF SIGNIFICANT LABORATORY ANIMAL DISEASE PROBLEMS OCCURRING IN VIVARIAL SETTINGS, AND THE DEVELOPMENT OF NEW ANIMAL MODELS USEFUL IN SOLVING BIOMEDICAL RESEARCH PROBLEMS. THE AWARD EMPHASIZES INDEPTH EXPERIENCE FOR THE LABORATORY ANIMAL SPECIALIST IN VARIOUS FUNDAMENTAL AND CLINICAL SCIENTIFIC DISCIPLINES. IN THE INITIAL PHASE, THE AWARDEE IS EXPECTED TO DEVELOP CAPABILITIES IN FUNDAMENTAL, APPLIED, AND/OR CLINICAL RESEARCH. IN THE FINAL PHASE, THE AWARDEE IS EXPECTED TO UNDERTAKE A MULTIDISCIPLINARY RESEARCH PROGRAM AIMED AT A BETTER UNDERSTANDING OF A LABORATORY ANIMAL DISEASE PROBLEM OR DEVELOPMENT OR UTILIZATION OF AN ANIMAL MODEL IN THE SOLVING OF A BIOMEDICAL RESEARCH PROBLEM.

ONE SUBJECT OF SPECIAL CONCERN IS THE PRESENT AND FUTURE STATE OF CLINICAL RESEARCH. A BURGEONING OF FUNDAMENTAL KNOWLEDGE IN THE PAST DECADE HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH. AND OF COURSE AN ELEMENT HERE COULD BE THE DEVELOPMENT OF INFORMATION IMPORTANT TO MEDICAL PRACTICE THROUGH CLINICAL RESEARCH AND CLINICAL TRIALS IN VETERINARY MEDICINE. I

WOULD CHALLENGE YOU TO LOOK AT THIS AREA AS ONE WHICH IF MORE CAREFULLY CONSIDERED BY YOUR PROFESSION MIGHT OFFER YOU NEW OPPORTUNITIES WHILE AT THE SAME TIME BRINGING GREATER CONTRIBUTIONS TO THE FIELD OF HUMAN HEALTH.

IN MY VIEW, THE TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT. SUCCESS FOR AN M.D. OR D.V.M. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MODERN SCIENCE.

ORGANIZATION

ANOTHER PRIORITY CONCERN IS TO PRESERVE THE ABILITY OF THE NIH TO ACCOMMODATE TO CHANGING DEMANDS OF BIOMEDICAL SCIENCE AND TO PROVIDE THE MOST EFFECTIVE MANAGEMENT. WITH GROWING PUBLIC

AWARENESS OF THE POTENTIAL FOR SUCCESSFUL INTERVENTION IN DISEASE PROCESSES, WE CAN EXPECT CONTINUED PRESSURE FOR ADDITIONAL, NARROWLY FOCUSED RESEARCH EFFORTS. IN RECENT YEARS, FOR EXAMPLE, THERE HAVE BEEN 10 PROPOSALS FOR NEW INSTITUTES (SLIDE 9) AND FIVE PROPOSALS TO TRANSFER TO NIH FUNCTIONS FROM OTHER PUBLIC HEALTH SERVICE AGENCIES (SLIDE 10). IN MY OPINION ADDITIONAL CATEGORICAL, DISEASE-SPECIFIC INSTITUTES AT NIH WOULD NOT CONTRIBUTE TO THE MOST EFFICIENT ADMINISTRATION OF RESEARCH AND WOULD ONLY LEAD TO INCREASED ADMINISTRATIVE COSTS AT THE EXPENSE OF FUNDING FOR RESEARCH. TO HELP RESOLVE QUESTIONS OF NIH ORGANIZATION, WE HAVE ASKED THE INSTITUTE OF MEDICINE TO MAKE AN 18-MONTH STUDY OF THE PRESENT STRUCTURE, TO EXAMINE ITS ADEQUACY AND EFFICIENCY AND TO DEVISE CRITERIA BY WHICH WE CAN EVALUATE AND DETERMINE NEED FOR FUTURE CHANGE. I URGE YOU TO PARTICIPATE ACTIVELY IN THIS EFFORT.

LEGISLATIVE ISSUES

THERE ARE SEVERAL ISSUES OF CONCERN TO NIH AND THE BIOMEDICAL RESEARCH COMMUNITY THAT ARE LIKELY TO BE ADDRESSED BY THE 98TH CONGRESS. ONE WILL BE THE ORGANIZATION OF NIH, AND SPECIFICALLY PROPOSALS TO ESTABLISH ADDITIONAL INSTITUTES OR TO TRANSFER AGENCY FUNCTIONS, AS I MENTIONED EARLIER. VARIOUS COMMITTEES WILL UNDOUBTEDLY BE SEEKING YOUR COUNSEL IN THIS MATTER AND I URGE YOU TO RESPOND IN AWARENESS OF THE OVER-ALL CONTEXT IN WHCIH WE ALL ARE WORKING AT THIS TIME.

Also before Congress in this session is the reauthorization of several NIH programs. Appropriation authority for the Cancer and Heart Institutes and the Medical Library Assistance Program of the National Library of Medicine expired at the end of fiscal year 1982. Other programs which will expire at the end of 1983, and will require authorization for operation in fiscal year 1984, include National Research Service Awards and several Advisory Boards, Centers and Information programs of the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases. I am concerned about attempts to amend further or revise our statutory authorizations. Section 301 of the Public Health Service Act has been the legislative cornerstone of our research activities for more than 40 years. It provides the continuity consistent with the long-term requirements of fundamental research.

We also expect reintroduction of legislation involving the use of animals in research and testing, about which you heard some details from Joe Held yesterday. Many other issues will come before Congress in various connections, such as indirect cost reimbursement, misconduct in science, ethical aspects of genetic engineering, and commercialization of research. All call for careful consideration and response. But we must be wary of the legislative quick fix. There is, of course, a long history of cooperation of NIH and the research community with the Congress.

To cite two examples: NIH, working with other PHS agencies, has drafted regulations governing misconduct in science and will issue them shortly. Similarly, we are taking steps, such as site visits to selected institutions that use laboratory animals in research, to determine whether institutional assurances reflect actual compliance with NIH guidelines and Federal Law.

CONCLUSION

I have mentioned but a few of the difficult issues we face; there are others, as you are all aware. I include on this list three that are of longer range. Foremost is the need to assure adequate levels of support for the research enterprise. Currently our award rate is 33 percent of approved applications. We believe an optimal level for progress would be 45-50 percent. In the context of the Federal budget the sums needed are not large. To achieve this goal we would need an additional $300-400 million per year for three years, and thereafter an annual budget of $5 billion, adjusted for inflation.

A similar problem exists in replacing or purchasing the increasingly sophisticatewd research instrumentation our laboratories now require. It is estimated that $20 million a year for five years is needed for the acquisition of large-scale

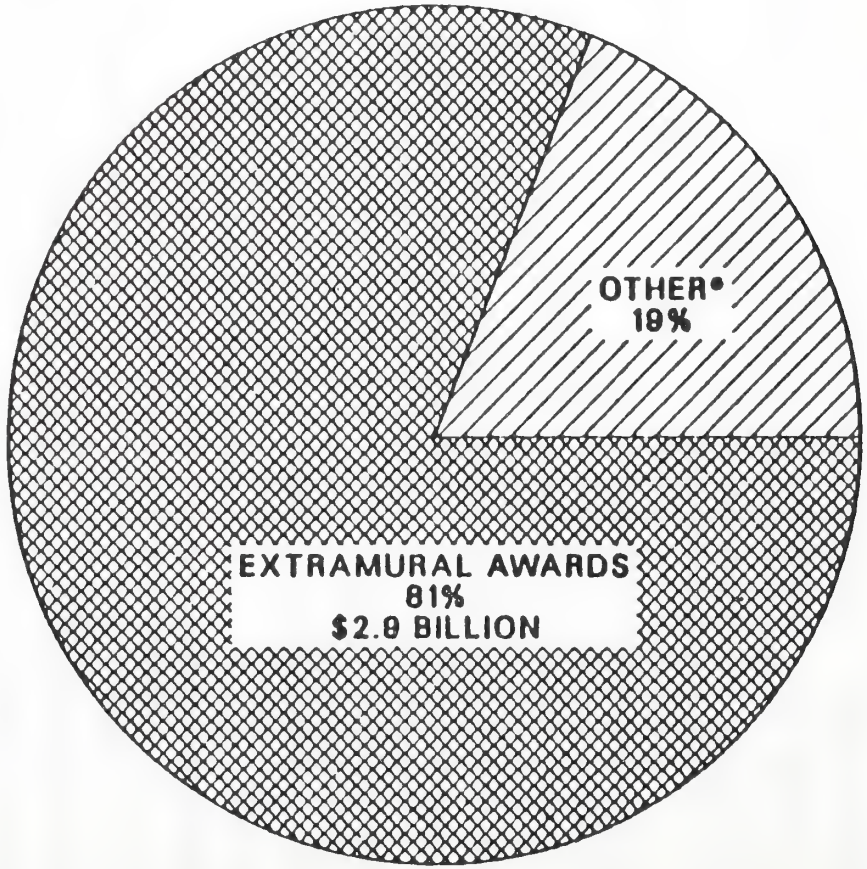
SHARED-INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE VIA RESEARCH GRANTS OF SMALLER INSTRUMENTS.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND, MORE RECENTLY, BY THE EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969. WE NEED TO HELP MODERNIZE AND TO CONSTRUCT NEW LABORATORIES.

I WANT TO EMPHASIZE THAT IT IS NOT POSSIBLE TO ACCOMPLISH THESE GOALS IN THE IMMEDIATE FUTURE. GIVEN THE CURRENT STATE OF THE ECONOMY, I BELIEVE NIH HAS FARED WELL. OUR BUDGET REPRESENTS A STRONG COMMITMENT BY THE ADMINISTRATION TO BIOMEDICAL RESEARCH. BUT I ALSO BELIEVE THAT AS THE ECONOMY IMPROVES IT IS IMPERATIVE TO INCREASE THAT LEVEL OF SUPPORT.

OUR PAST HISTORY OF COOPERATION IN THE EVOLUTION OF THE NATION'S GREAT BIOMEDICAL RESEARCH ENTERPRISE GIVES ME CONFIDENCE IN OUR ABILITY TO SOLVE CURRENT PROBLEMS THROUGH WORKING TOGETHER. WHILE WE ALL ENCOURAGE THE INTENSE COMPETITION THAT DRIVES SCIENTIFIC DISCOVERY, WE SHOULD VIEW OURSELVES AS COLLABORATORS IN OPERATION OF THE SYSTEM THAT SUPPORTS THE RESEARCH EFFORTS. WE ARE VITALLY CONCERNED FOR THE HEALTH AND STABILITY OF THE INSTITUTIONS IN WHICH SO MUCH OF THE ESSENTIAL RESEARCH IS CONDUCTED, JUST AS YOU ARE FOR THE SUCCESS OF NIH. ON BEHALF OF NIH, I INVITE YOUR ADVICE, COUNSEL AND SUPPORT IN THE MONTHS AHEAD.

EXTRAMURAL AWARDS MAKE UP 81% OF THE NIH BUDGET
FISCAL YEAR 1982

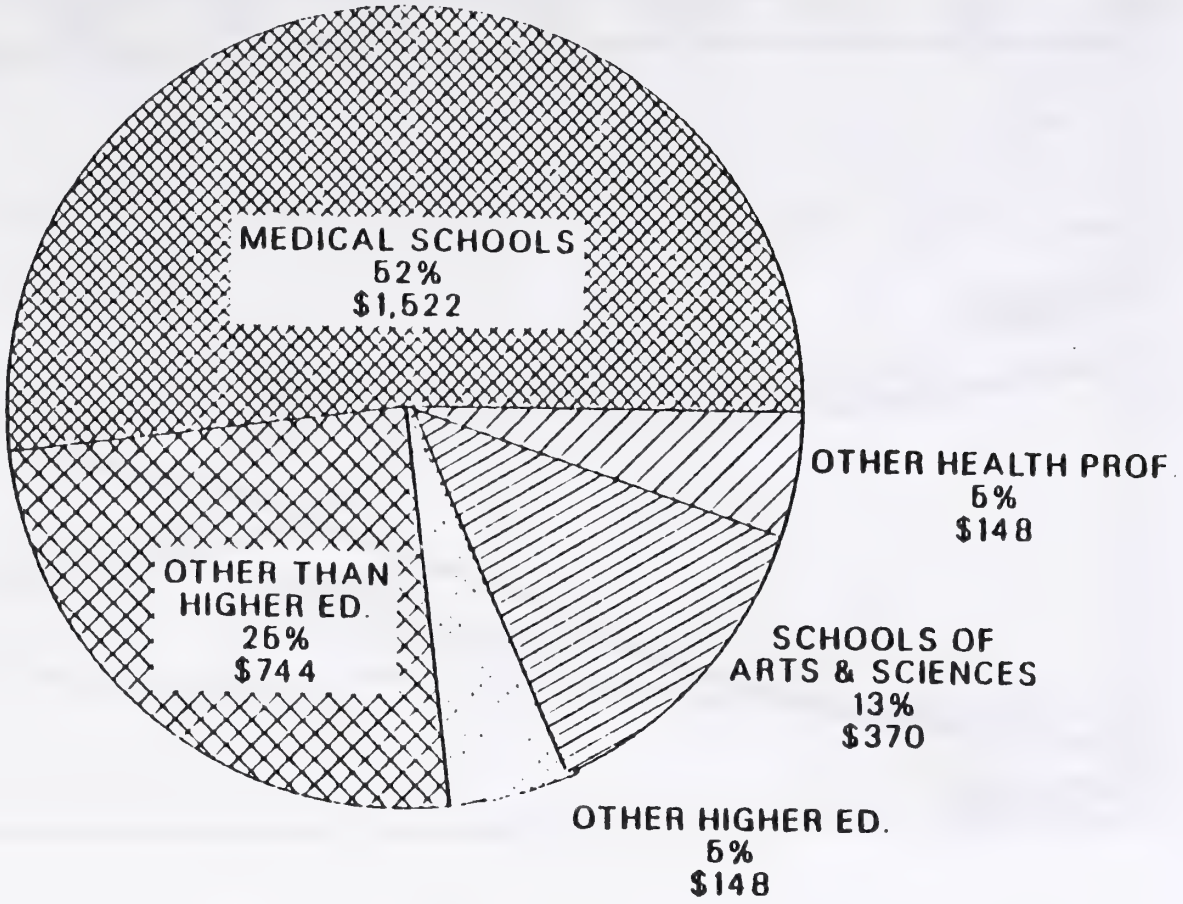


TOTAL - $3.6 BILLION

*INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH.

(CURRENT DOLLARS IN MILLIONS)

'75	51%
'76	49
'77	49
'78	51
'79	52
'80	51
'81	52



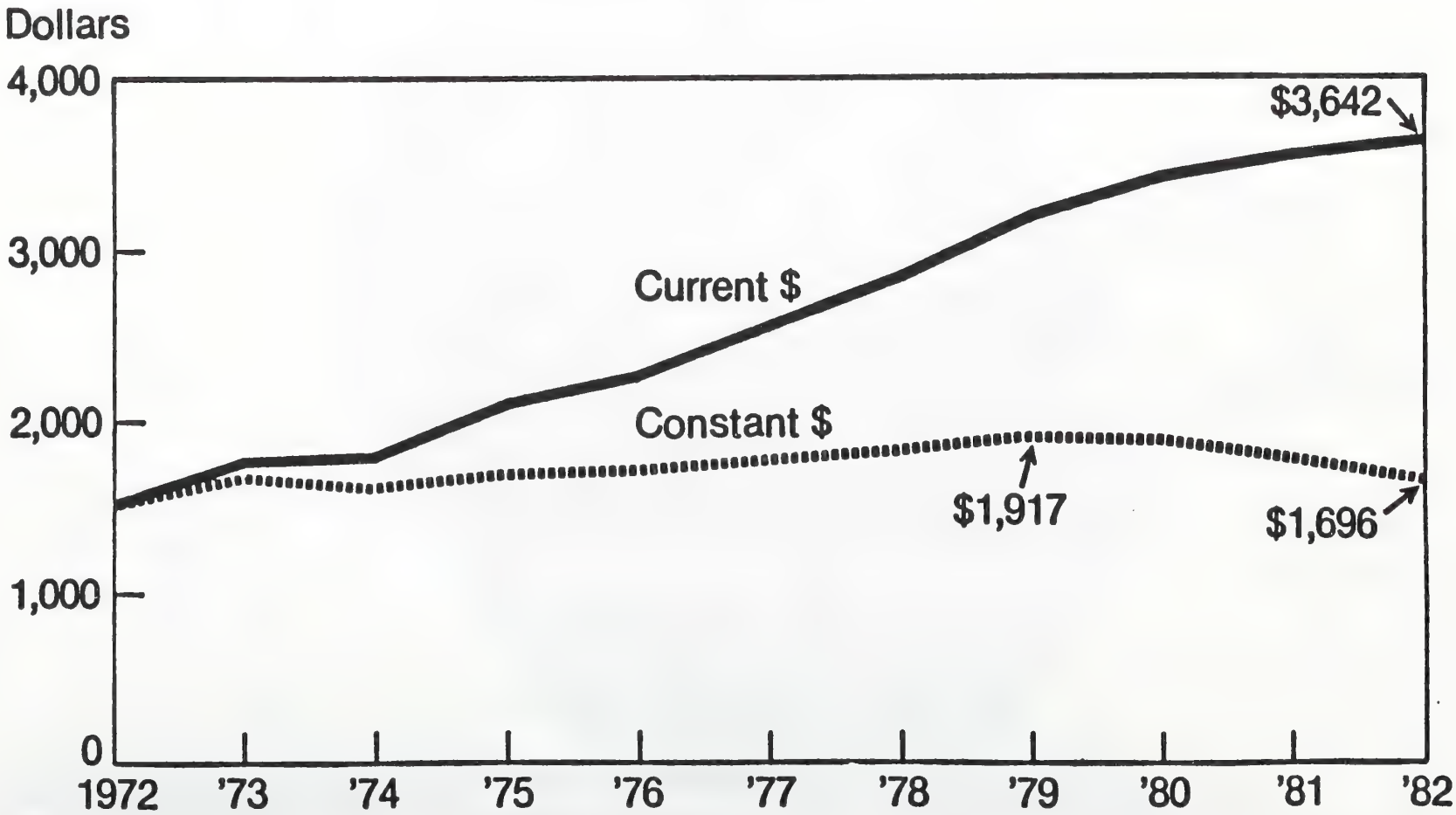
FY 1982*

$2,933 MILLION

*PRELIMINARY.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH

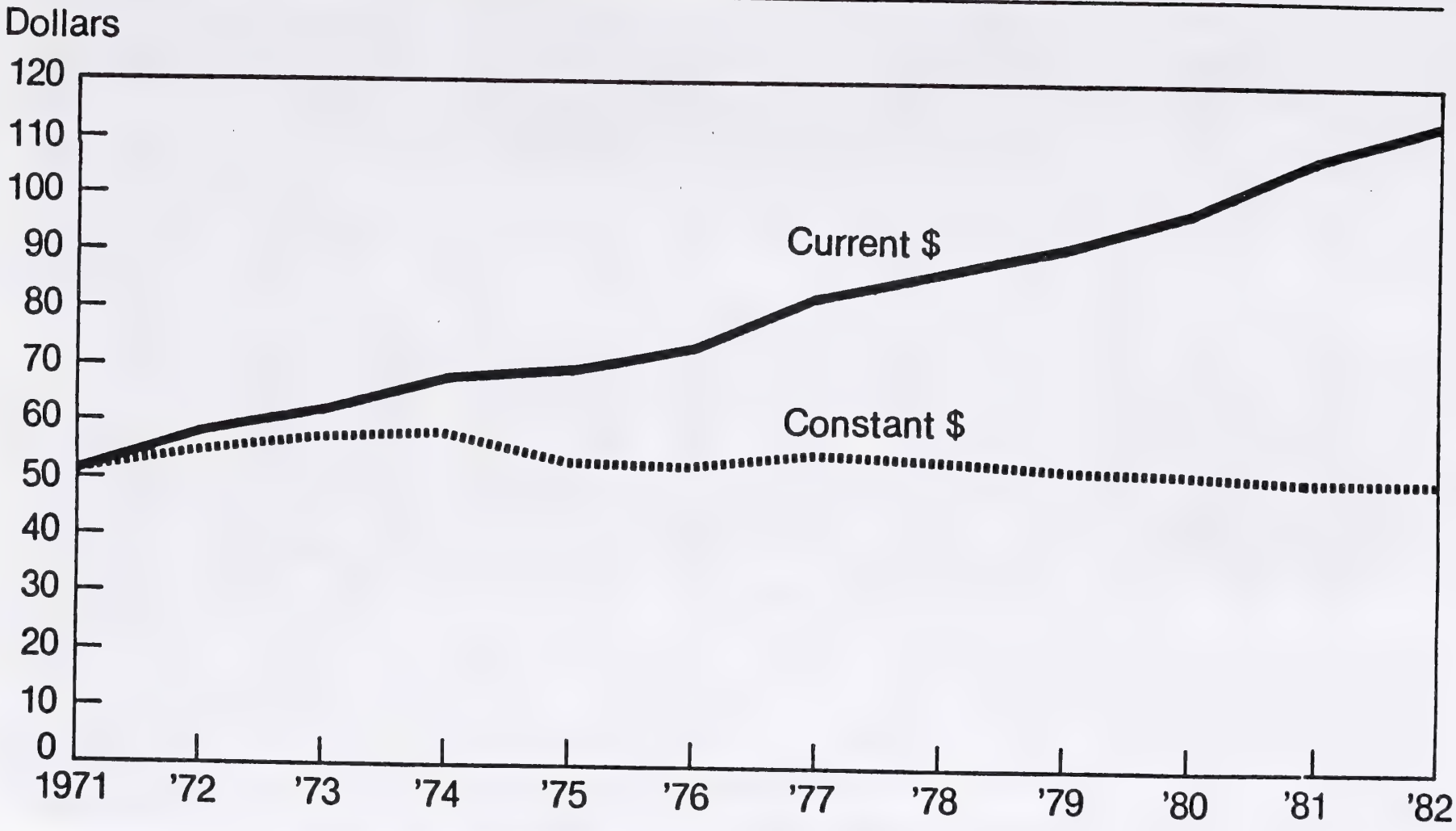
Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)

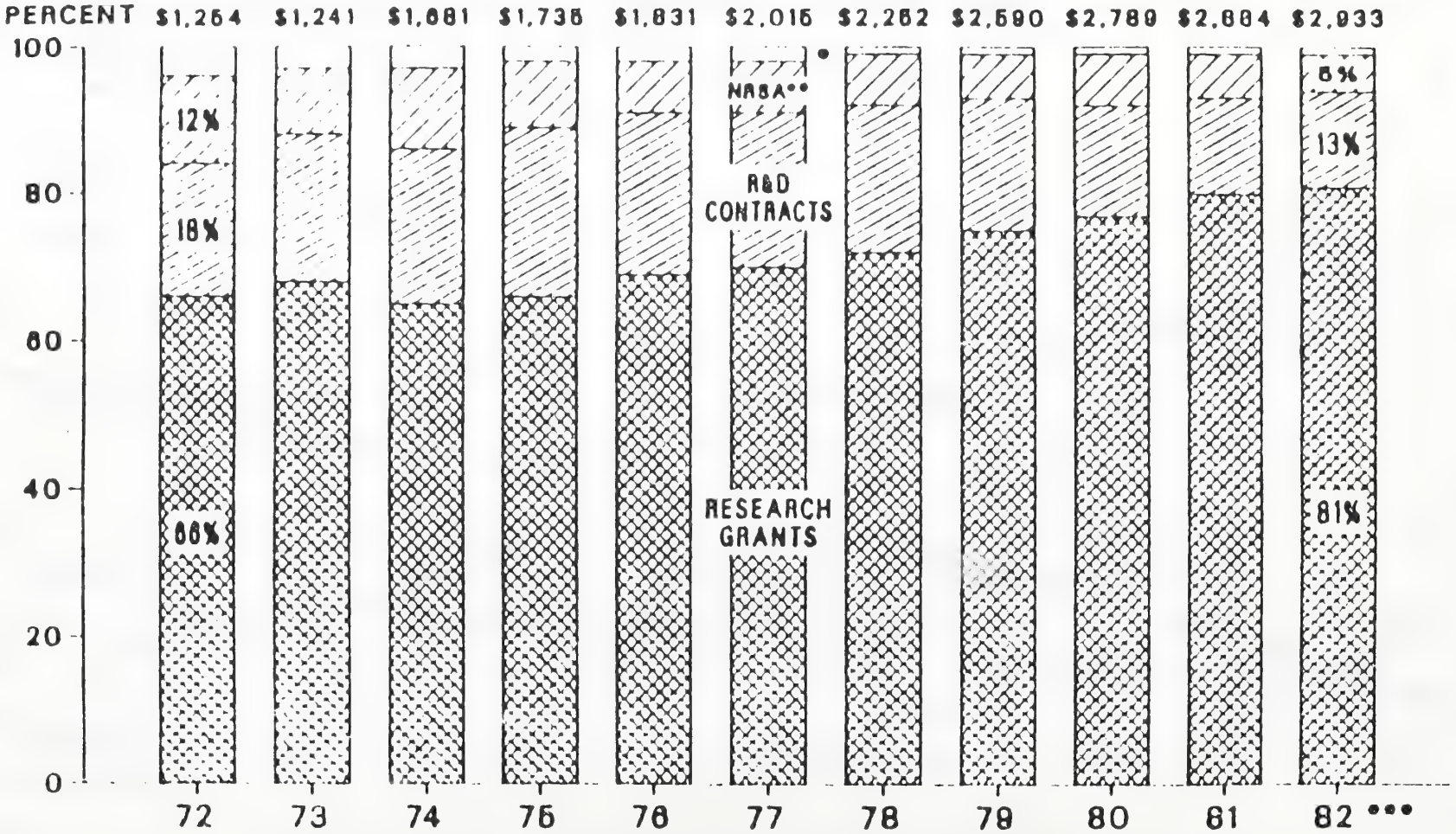


Average Research Project Grant, 1971-82

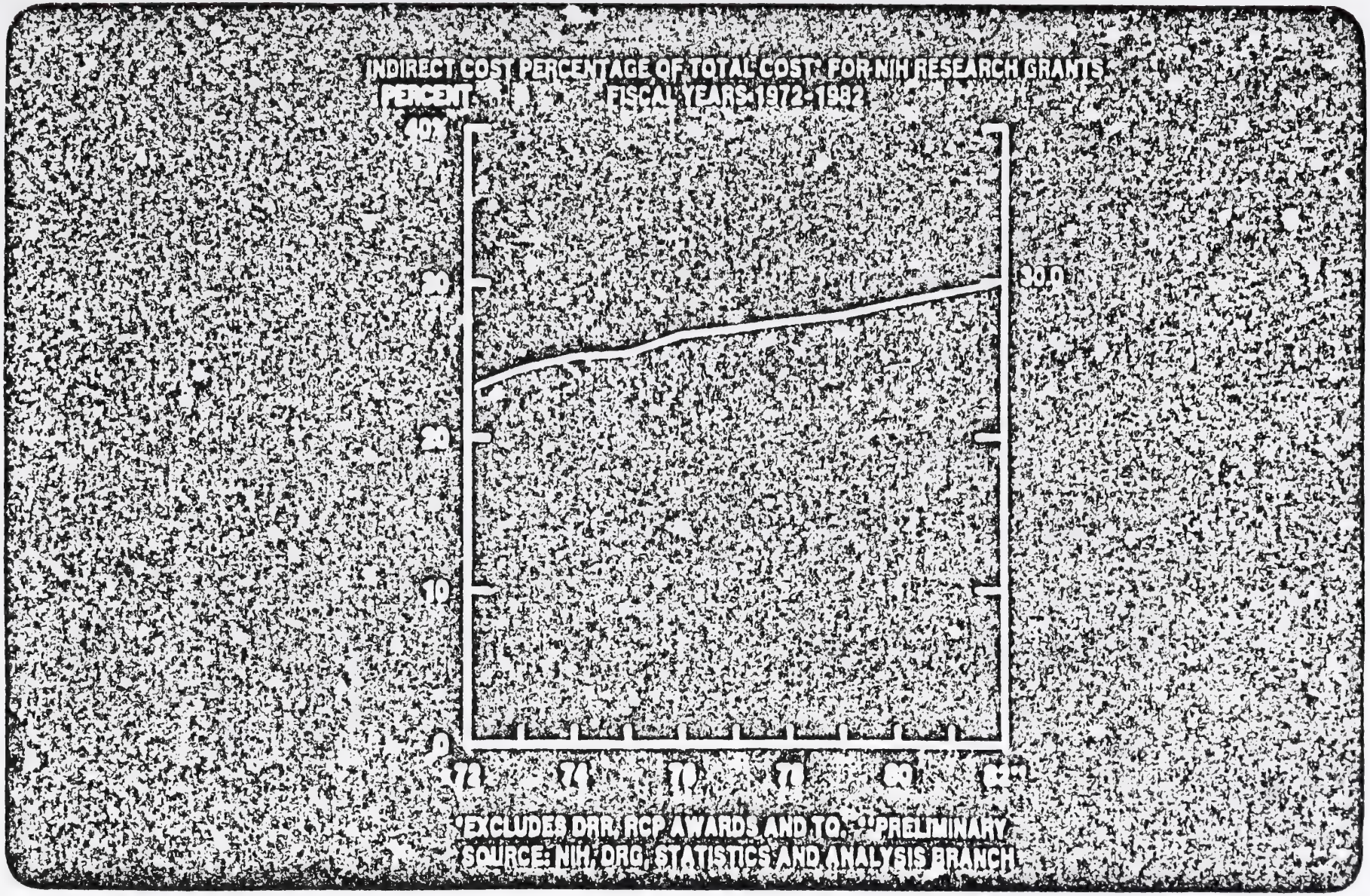
In Current and Constant Dollars (Thousands)



ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1982
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE: EXCLUDES TQ. *INCLUDES CONSTRUCTION, CONTROL, AND MEDICAL LIBRARY GRANTS.
**INCLUDES PRE-NRSA TRAINING. ***PRELIMINARY.
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH


INDIRECT COST PERCENTAGE OF TOTAL COST* FOR NIH RESEARCH GRANTS
FISCAL YEARS 1972-1982
PERCENT
30%
20
20
10
0
30.0
72
77
78
79
80
82
*EXCLUDES DRR, RCP AWARDS AND TO. **PRELIMINARY
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

NIH Support for Training In Laboratory Animal Science and Medicine

Administered by: Division of Research Resources
Animal Resources Program

Funded in FY 82: 9 Institutional Training Programs
31 Trainees
2 Individual Postdoctoral Fellows

SERCA* Program for Veterinarians

Administered by:	Division of Research Resources Animal Resources Program
Purpose:	To Develop Multidisciplinary Veterinary Researchers
Length of Award:	5 Years
Initial Phase (3 Years):	Career Development with Mentor
Final Phase (2 Years):	Pursuit of Research Project

*Special Emphasis Research Career Awards

Unsuccessful Proposals for Major Organizational Change at NIH

Proposed Institutes
National Institute for International Medical Research (L)
National Institute of Emphysema and Respiratory Disease (L)
National Kidney Institute (L)
National Institute of Marine Medicine and Pharmacology (L)
National Lung Institute (L)
National Sickle Cell Anemia Institute (L)
Institute for Research on Dysautonomia (L)
National Institute for Population Research (L)
National Institute of Diabetes, Endocrinology and Metabolic Diseases (L)
National Institute of Arthritis and Musculoskeletal Diseases (L)

L — Proposed Legislatively
A — Proposed Administratively

Unsuccessful Proposals for Major Organizational Change at NIH

PHS Components Proposed for Transfer to NIH

National Institute for Occupational Safety and Health (L)

Alcohol, Drug Abuse and Mental Health Administration (A)

National Center for Health Services Research (L)

National Center for Health Statistics (L)

National Institute of Mental Health (L)

L — Proposed Legislatively
A — Proposed Administratively

TALKING POINTS

RESEARCH UNIVERSITIES NETWORK (RUN) BREAKFAST

Ramada Renaissance Hotel
8:30 a.m., March 16

INTRODUCTION

- o Long-standing federal-academic partnership in biomedical research faces serious problems to be addressed in a collegial manner.

- o The partnership:

  --Federal government supports estimated 90 percent of basic biomedical research in U.S.

  --More than 60 percent of R&D at universities and medical schools funded by NIH.

  --Extramural awards in FY 1982 were 81 percent of NIH budget and 52 percent went to medical schools.

- o Partnership has thrived, solved problems in past. Main current problem is to operate within tight budgets and economy.

BUDGET

- o Past trends:

  --1972-1982: 15 percent increase in constant dollars.

  --But, indirect costs during period almost exactly consumed the rise, so funds to support direct research costs essentially same in 1983 as in 1972.

  --Between 1979 and 1982, budget fell by 12 percent, rose by 4 percent in 1983 for net decrease of 8 percent.

- o FY 1984 proposed NIH budget requests $4.077 billion.

  --That would be a $73 million, or 1.8 percent, increase over FY 1983, for which inflationary rate of 5 percent predicted.

- o NIH budget in steady state for more than a decade; can't expect dramatic increase in near future.

  --Have accommodated to constant budget by shifting funds among mechanisms to support maximum number of research proposals and trainees

POLICY AND PROGRAM ISSUES

- o Steady-state resources inevitably intensify competition for support in all areas of NIH responsibility.

- o In awareness of multiple responsibilities and fiscal constraints, highest priorities are:

  --To sustain maximum stability in investigator-initiated research project base.

  --To support training of optimum number of new investigators.

  --To organize the agency for maximum efficiency.

STABILIZATION

- o Importance of fundamental knowledge and investigator-initiated research.

- o Objective: provide steady and predictable level of support for investigators and trainees.

  --We have succeeded in recent years: 1981 support for 5,140 new and competing grants; 1982 support for 5,027 grants; 1983 support for 4,914 grants.

  --Also supporting 9,696 trainees in 1983.

- o To achieve those levels, had to shift funds from some mechanisms, notably clinical trials and initiatives, such as research centers.

- o Fiscal year 1984 budget still being negotiated with OMB.

  --Without additional budgetary shifts, President's budget would support 3,676 competing awards and 9,105 trainees.

- o Problem: Given finite resources, stability in one of several elements causes de-stabilization in others.

  --If current rate of increase in percent of NIH budget for extramural grants were to continue, would reach 100 percent around 1983.

- o Pressures expected to intensify because of some trends:

  --Average cost per grant grown faster than rate of inflation.

  --Indirect costs increased faster than direct costs: Between 1972 and 1982, direct costs increased by factor of 3.6; indirect costs rose almost five-fold.

--Clear reflection of this differential in 1982: of $76 million additional funding for extramural grants over 1981, $34 million, or 46 percent, went to indirect costs.

o Controversy over indirect costs continues; note reaction to HHS draft report and February 17th meeting.

THOUGHTS FOR ACADEMIC COMMUNITY

o Help in cutting overhead:

--Competing applications were 15,732 in 1981 and 16,989 in 1982. That compares with 8,600 in 1972.

--In 1982, 25 percent of applications were resubmissions; twice the number 3-5 years ago.

--Trend toward multiple applications per investigator.

o Flooding the system does't necessarily pay off:

--In 1981, we found the faculty that submitted least number of applications (155) was awarded largest number of grants (83).

TRAINING

o Diminishing proportion of physicians engaging in NIH-supported research.

o Success rates, in declining order: MD/PhD, PhD, MD.

o Of 2,800 positions in clinical training recommended by NAS, 900 now filled by PhDs, compared to 450 several years ago.

o Considering new program, perhaps: Physician-Scientist Training Program for three years of full-time research training and stipend that matches residency level.

ORGANIZATON

o Pressure for new institutes: in recent years, 10 institutes, 5 transfers proposed. Current pressures for Arthritis Institute.

o IOM study. Hope to persuade Congress to hold off until study complete.

SOME ISSUES EXPECTED IN 98TH CONGRESS

o NIH reauthorization (House and Senate versions).

o Animal Welfare

o Indirect costs/salary support

o Misconduct in science

-fpw-3/11/83

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-fpw-3/11/83

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

It is a pleasure to welcome you here this morning to the National Institutes of Health and to this "U.S.-Japan Workshop on Research in Inborn Errors of Metabolism." I am particularly pleased to see so many familiar faces, as well as a number of new ones, and I extend to each of you our very warmest greetings. Your interest in this workshop and willingness to participate in it were determining factors in assuring its co-sponsorship by several NIH Institutes and Divisions. This co-sponsorship also reflects the fact that research on inborn errors falls within the purview of several NIH Institutes. On their behalf, let me also extend a special welcome to our guests from Japan. It is good to have you here with us, and I am confident that your participation in this workshop will be fruitful and productive.

As you know, inborn errors of metabolism include over 250 rare, or very rare, diseases. Their impact on public health becomes particularly significant through the extensive mortality, morbidity, and psychological anguish they collectively cause. Inborn errors do not recognize national boundaries and their prevention, alleviation, and even elimination in our lifetime are goals worthy of maximum international efforts.

Inborn errors present many difficult challenges to those seeking to understand their pathophysiology. Many of these difficulties are associated with the very low incidence of specific diseases, and therefore to the very

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* Presented at the Opening of the U.S.-Japan Workshop on Research in Inborn Errors of Metabolism, Building 31C, Conference Room 6, on March 19, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

limited availability of subjects, tissues, cells, enzymes, and other research resources necessary for both basic and clinical studies. Broadening the science base through initiation of international collaborations, in research areas of common interest, is a major objective of this workshop. We hope that your discussions here might identify new mechanisms to help overcome some of these difficulties.

The many outstanding research achievements of our Japanese guests are well known to all of you. The "International Symposium on Neonatal Screening for Inborn Errors of Metabolism" that was recently held in Tokyo further signifies the commitment that Japanese scientists have for preventing, treating, and understanding the etiology and pathogenesis of these diseases.

Here at NIH, in our intramural program, there is also a long-standing tradition of excellence in the study of inborn errors. Numerous laboratories have devoted years of effort to obtaining a better understanding of various inherited metabolic disorders. (Elaborate on personal experiences . . .)

NIH is also providing the extramural community with significant support for research related to inborn errors, primarily through the investigator-initiated research project grant mechanism. This mechanism of support, which represents the core of the NIH extramural programs, provides individual investigators with the flexibility to pursue promising scientific opportunities wherever they might lead. Through this mechanism, the creativity of investigators throughout the biomedical sciences has been translated into many of the remarkable research advances that we have seen in recent years.

Today, opportunities in research grow out of what was termed a "profound development in medical science" by Dr. Arthur Kornberg, Nobel Laureate and member of the NIH Director's Advisory Committee. In a recent address, Dr. Kornberg described a "confluence of the many discrete and previously

unrelated medical science subjects into a single, unified discipline. Anatomy, physiology, biochemistry, microbiology, immunology, and genetics have now merged and are expressed in a common language of chemistry," he said. This is especially true in the study of inborn errors of metabolism.

Research results presented and discussed here today and tomorrow will be a testimony to the power of recently developed research tools and techniques. They will also be testimony to the interactive nature of this research field, and the outstanding potential that it holds for future research advances.

Interest in, and support of, research in inborn errors of metabolism rests upon a solid foundation at NIH which is reflected in the broad base of this workshop's co-sponsors. Representatives of various NIH Institutes and Divisions now meet periodically to review issues of relevance to this research field. I am confident that the discussions at this workshop will assist this group, both in further identifying the needs and opportunities for research in inborn errors, and subsequently in developing responsive program initiatives.

In closing, let me simply reiterate that we are very pleased to host this meeting here today, and I share with you the hope that the objectives of this workshop will be fully realized.

Thank you.

INTRODUCTORY REMARKS FOR DR. BRANDT*

by

James B. Wyngaarden, M.D.**

As Assistant Secretary for Health, Dr. Brandt directs the activities of the Public Health Service which includes the Health Resources and Services Administration, the Centers for Disease Control, the Food and Drug Administration, the Alcohol, Drug Abuse, and Mental Health Administration, and the National Institutes of Health. He advises and assists the Secretary of Health and Human Services on health policy and on all health-related activities of the Department.

Before being sworn in as Assistant Secretary on May 14, 1981, Dr. Brandt had for eleven years been associated with the University of Texas: seven years as Executive Dean of the University's Medical Branch in Galveston; and, for the last four years before coming to Washington, as Vice Chancellor for Health Affairs of the University system.

From 1962 to 1970, Dr. Brandt was at the University of Oklahoma Medical Center, first as Director of the Medical Research Computer Center and later as Associate Dean.

My experience in working with Dr. Brandt for the past year has convinced me that he operates on a fast track--but this isn't new for him.

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* Program of Human Resource Management Training on Employment of Disabled Individuals, PHS Handicapped Employees Committee, Lister Hill Auditorium, March 29, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

He graduated from the University of Oklahoma with a bachelor's degree in mathematics when he was 20. He had a master's in mathematics from Oklahoma State at 21, and earned his M.D. at the University of Oklahoma at 26--and his Ph.D. there before he was 30.

BIOMEDICAL RESEARCH SUPPORT: CONCERNS AND ISSUES*

by

James B. Wyngaarden, M.D.**

When Nathan Stark and John Hogness invited me to participate in this panel, they suggested that I discuss pertinent portions of the proposed NIH budget and give a perspective on NIH-related legislation now before the Congress. As far as the budget is concerned, their timing was exquisite for on the day after tomorrow, we will begin our appropriations hearings for the 1984 budget. On Tuesday and Wednesday, the NIH Bureau, Institute, and Division Directors and I will testify before the Senate Appropriations Subcommittee, and the following week we will begin our House hearings. If anything, the timing was a bit too precise in that some of the details of the budget are still in the process of final approval and official transmission to the Appropriations Committee. Permit me to sketch in a bit of background.

Last fall when I attended and spoke to your meeting at Kiawah Island, it was the next to last day of fiscal 1982. At that time, on the eve of fiscal 1983, the Congress was considering the President's budget request for NIH that called for a total of $3.64 billion--a budget which would permit funding of 4,100 new and competing grants. Among other features of the budget, there was a requirement that indirect costs be reduced by 10 percent across the board. The 1983 appropriation was not passed and signed until

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* Presented at the Spring Meeting of the Association of Academic Health Centers, Hyatt Arlington at Key Bridge, Arlington, Virginia, April 10, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

mid-December, and then it was in the form of a continuing resolution. As it turned out, the amount finally approved for the NIH came to just over $4 billion enabling us to make about 4,900 new and competing grant awards--and the terms of the appropriation require us to pay full indirect costs.

Now, as I meet with you six months later, our attention is focused on fiscal 1984 and if the image is rather fuzzy and blurred here and there, it is the result of a series of happenings that even in the somewhat turbulent and confusing context of budgets must be called an unusual turn of events.

As you know, when the President announced his 1984 budget requests on January 31, the total proposed for NIH was $4.077 billion, an increase of 1.8 percent over the current level. As usual, the NIH prepared detailed information on how the proposed total would be distributed among the constituent units and funding mechanisms. It was our estimate that the number of new and competing grants that could be awarded under the proposed budget would be 3,676--substantially fewer than the nominal stabilization level of 5,000. In the hectic last few days before the budget was submitted, the NIH plan for use of the funds was tentatively approved and filed with the Appropriations Committee as a draft. Accompanying the draft was a letter from Secretary Schweiker, which incidentally was among his last official acts, having been signed on February 2. His resignation became effective on February 4.

Let me read you Secretary Schweiker's letter. He said:

"I want to advise you that it is the Administration's policy in FY 1984 to fund 5,000 new and competing research grants at the National Institutes of Health (NIH). Although the enclosed justification materials, which are being furnished to you in draft format to provide program information, do

not reflect this policy, the Administration's position is to fund this level of new and competing grants.

"In part due to the unavoidable timing of Congressional action on FY 1983 appropriations and because of the internal timing of FY 1983 budget development in the Executive Branch, we could not include the appropriate adjustments to the FY 1984 President's budget. We are now assessing the resource adjustments necessary to achieve this policy given FY 1983 Congressional action. Discussions are currently under way between the Department and the Office of Management and Budget on this matter.

"We will inform you of the necessary changes required in our request to institute the 5,000 grant policy as soon as these discussions are concluded and final decisions reached."

The final decisions referred to by the Secretary were reached just over two weeks ago--namely, that no additions would be made to the original budget estimates for the NIH. This meant that the request would stand at $4.077 billion and that adjustments would be made in other program mechanisms to permit the award during 1984 of 5,000 new and competing grants.

The complex adjustments required by these decisions are now in the final stages of review and approval, and consequently I am not in a position to discuss the 1984 budget in detail today.

There are a number of other important issues, however, that soon will be brought to decision or at least to debate in the Congressional consideration of reauthorization of the National Cancer Program, the National Heart, Lung, and Blood Institute, the National Library of Medicine, the National Research Service Awards Program, and certain special programs on diabetes, arthritis, and digestive diseases.

The most comprehensive reauthorization bill is H.R. 2350 (Health Research Extension Act of 1983) which would recodify all existing authorities for NIH programs and create in Title IV of the Public Health Service Act a self-contained exclusive source of authority replacing any reference to Section 301, the General Research Authority of the Public Health Service, with a combination of enumerated authorities and general delegations provisions. Assistant Secretary for Health Ed Brandt testified on H.R. 2350 February 25, stating our position that such extensive changes in the language of Title IV would disrupt the orderly management and operating procedures of NIH as a whole and of the individual Institutes. He stated that "We also believe the degree of detail and specificity in the bill would create organizations and procedures that are too rigidly defined and, in fact, represents an attempt to micromanage the NIH."

The Waxman Bill is a kind of catalog of important issues facing the NIH and the biomedical research community at this time. In that sense, I will use it as a framework for discussion of matters to which we as partners in the research enterprise must give our attention and cooperative effort, recognizing that the legislative proposals reflect genuine concerns about the way in which we have carried out our vitally important mission. But we are increasingly concerned about such highly specific legislation which in part results from increasing competition among scientists and lay advocates of specific disease research programs who seek target funding or specific legislative priority.

Over the past 10 years, there have been over ten legislative proposals to establish new NIH Institutes and numerous proposals to set aside funds or otherwise to place special emphasis on certain programs related to specific diseases or systems of the body. The unfortunate consequence of these

mandates is to limit increasingly the ability of NIH to support a broad range of research projects directed not at narrow and isolated components of public health but at the whole spectrum of activities designed to understand, prevent, and treat disease.

H.R. 2350 exemplifies this problem by requiring specific earmarks of funds or special emphasis or activities for:

- Health Promotion and Disease Prevention Centers
- Cancer Centers
- Kidney and Urologic Diseases Research Centers
- Research in Spinal Cord Regeneration
- Operation of the National Center for Health Care Technology
- Sickle Cell Disease Centers
- Pertussis Vaccine Study
- Study of Personnel for Health Needs of the Elderly
- Study of Commercial Use of Biomedical Research Results
- Interagency Committee on Learning Disabilities
- Research Into Diet Therapy in the Treatment of End-Stage Renal Disease
- Research in the Relationship Between Diet and Cancer
- Research in Developing Research Methods That Reduce the Use of Animals or Minimize Animal Pain
- Mental Retardation Centers
- National Commission on Orphan Diseases

From a broader perspective, a number of the provisions in the bill seem to stem from doubts that the current structure of the NIH is adequate to respond to either the evolution of science or the changing nature of health

care problems. Some of the changes go beyond structural proposals and verge on a reorientation by expanding and modifying the agency's mission.

NIH's mission is clear and unambiguous--to improve the health of the nation through the conduct and support of research and, in particular, the generation of knowledge. NIH does not provide health services, and its regulatory responsibilities are limited to setting standards for human subjects research. The current organization of NIH, which has evolved over a period of 50 years, is sufficiently broad to accommodate changes in scientific direction and scope and to collaborate with other PHS agencies in transferring knowledge into the health care system. We are concerned, for example, about the impact on the research programs of the NIH of proposals that would require the establishment of statutory preventive-related staff offices in each Institute and create 25 prevention research and demonstration centers.

Prevention of disease and disability is the ultimate goal of all NIH research programs, but research into prevention must rest on a firm scientific base and be closely linked with other research efforts. Where such a base exists, serious attention is being given to research into prevention of disease. For some Institutes and in some disease areas, prevention research is more than fully warranted and, in fact, is being carried out. In others, the time is not ripe and the proposed organizationsl sturcture is inappropriate. What is needed is the flexibility that now exists for the optimum deployment of scientific and financial resources.

Other provisions of the reauthorization bill that would move the National Center for Health Services Research, the National Center for Health Statistics, and the National Institute of Occupational Safety and Health to

the NIH are bound to have a serious effect on the ability of the NIH to carry out its central mission.

A major proposal within the reauthorization bill would create a new Institute--the National Institute of Arthritis and Musculoskeletal Diseases. The Department has emphatically opposed the creation of this separate Institute for several reasons. The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases now conducts and supports highly effective programs of basic and clinical research and research training related to arthritis and musculoskeletal and skin diseases. There is no evidence that the arthritis program is receiving less than an appropriate allocation of resources or attention within NIADDK. To the contrary, it is the fastest growing research program area within that Institute and among the fastest growing programs throughout NIH. The facts simply do not bear out the theory that the only way to increase resource allocation to arthritis-related research is to change the organizational structure of NIH.

In spite of our concerns about the provisions I have mentioned, we are not opposed to carefully considered changes in the structure of NIH. We recently negotiated a contract with the Institute of Medicine of the National Acadmey of Sciences for a comprehensive evaluation of the organization of NIH. We have asked IOM to:

- Conduct a thorough systematic review of NIH's organizational evolution and development and to examine the present structure of NIH and its underlying rationale;

- Examine NIH's present approach to those issues that cut across internal organizational lines and develop alternative approaches for consideration; and

o Develop a rationale and the criteria on which to base future changes in the light of scientific developments and economic conditions.

Accordingly, we believe it is premature to legislate extensive organizational changes before the IOM study is completed and its recommendations are reviewed.

One provision of the bill that I know to be of interest to you would require the payment of indirect costs as prescribed by Office of Management and Budget Circular A-21, which defines the costs allowable for reimbursement.

Indirect costs are also a concern of the House and Senate Appropriations Committees. After last year's budget hearings, the House Committee requested a report from the Department setting forth conclusions and appropriate recommendations to the Committee for discussion in connection with the 1984 budget request.

The report is now in the final stages of consideration within the Administration and has not yet been submitted to the Appropriations Committee. For that reason, I am not in a position to state the recommendations it contains. I can tell you, however, that the "Blue Sheet" a few days ago reported the options said to be presented and discussed in the report. Let me read them:

Option 1: An across-the-board 10 percent reduction as opposed (and rejected) as a part of the 1983 budget request.

Option 2: Capping selected indirect cost components--as, for example, the costs of Departmental administration.

Option 3: Establishment of a standard fixed allowance coupled with deregulation in the form of a significant reduction in record keeping requirements as, for example, reduction of the time-and-effort accounting and elimination of cost-sharing documentation.

Option 4: Establishment of a fixed allowance based on each institution's historical level. Each grantee would be assigned an individualized allowance for indirect costs by establishing an institution-specific indirect cost ratio based on the experience of recent years at that institution. This option would also include the deregulation feature proposed under the fixed allowance option.

For the long term, the options suggested include a continuation of one of the short-term options or a redefinition of reimbursable indirect costs, or finally to offer the grantee institution a choice of a fixed allowance or a negotiated rate based on standardized cost categories.

The issues associated with each of the policy options are complicated and controversial. It will be necessary to assess with care the impact of any proposed change to insure that it is as equitable as possible and that it takes into account the many differences among grantee institutions.

This is a sensitive subject--one that will require much more consultation and mutual understanding among the affected parties if we are to develop practical solutions to the problems of reimbursement for indirect costs.

Let me turn now to two other matters about which I think the NIH and the institutions are in agreement. Both of these issues are the subjects of amendments which have been added to the NIH reorganization bill. The first issue can be stated as a question. How can the biomedical research

community and particularly the NIH respond to a public health emergency when research is the key to even the beginning steps in coping with the emergency?

Recently the press, radio, and television have been devoting a substantial amount of attention to the outbreak of a new disease of great virulence--acquired immune deficiency syndrome (AIDS). It is a frightening problem, indeed--currently more than 1,300 cases have been reported in the United States since the disease was first identified in the spring of 1981, and the number of new cases reported each week is on the increase. The case fatality rate exceeds 60 percent for cases diagnosed over one year previously. Some researchers believe no one survives AIDS.

While the cause of AIDS is not known, most investigators believe that it is carried by an infectious agent, in all likelihood a virus. Seventy-five percent of AIDS patients are young, white, urban homosexuals or bisexual men who are very active sexually--a smaller group of AIDS patients are heterosexual but users of intravenous drugs; and it appears that the disease can be transmitted through transfusions of blood and blood products. Obviously, it is critically important that means be found as quickly as possible to arrest the spread of the disease, to restore the compromised immune systems of AIDS patients, and to devise a reliable screening test for blood and blood products.

The NIH has come under heavy criticism from the gay rights community, particularly with the charge that we have not made a commitment for adequate research and that we hve been dragging our feet to resist shifting and using funds for AIDS research. The allegations are not true. We expect to spend at least $98.5 million this year and almost $12.5 million next year on research related directly to AIDS.

In the last year or so, there has been a marked upsurge in activity by public groups attacking the use of animals in research. We are seeing for the first time joint efforts by various animal rights groups--bringing together the more traditional groups with the more extreme activist organizations.

Their public relations and emotional media campaigns have been skillfully carried out and seem likely to be on the increase. The Congress has been bombarded by mail and in the face of such constituent pressures, it is almost inevitable that legislation on the subject will emerge.

We must make the public aware of the critical impportance of animal research to improvements in human health care and disease prevention. We must also demonstrate by action our concern for the ethical and humane treatment of animal subjects of research. Unless we can get both of these messages across to the general public and to the Congress, I believe we will see a series of progressively restrictive legislative measures governing the use of animals.

Many of us may be reminded of the vigor of the animal rights groups two weeks from today on April 24 when demonstrations are scheduled at various research centers around the country in observance of World Laboratory Day.

In the past 20 minutes, I have opened a number of subjects of mutual interest--and have done little more than to suggest them as topics for fuller discussion. When the question period comes, I would be glad to speak more fully about the issues that have been brought up or others that may be suggested by them.

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